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Report for the PERIOD

July 1, 1951 --- December 31, 1952

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U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service

FOREWORD

Because of a decision to convert this detailed program report from a fiscal year to a calendar year basis, this "annual" report actually covers a period of eighteen months, from July 1951 through December 1952.

The need for compilation of such materials in a single publication has been stated on many occasions. It is prepared for the express purpose of communication - between research workers, between research program areas, and between the National Institutes of Health and other components of the Public Health Service and the U. S. Department of Health, Education, and Welfare.

In the following pages, you will find specific information concerning every major activity of the National Institutes of Health. The report has been distributed among NIH staff, with a copy to each division of the Public Health Service and to each major constituent and regional office of the Department. A limited number of copies is available on request from the Scientific Reports Branch, National Institutes of Health.

W. H. Sebrell, Jr., Director
National Institutes of Health

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NATIONAL INSTITUTES OF HEALTH

Report for the Eighteen-Months Period

July 1, 1951 --- December 31, 1952

William H. Sebrell, Jr. ....Director

James A. Shannon ....Associate Director

C. J. VanSlyke ....Associate Director

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NATIONAL CANCER INSTITUTE

J. R. Heller, Director

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NATIONAL CANCER INSTITUTE

July 1, 1951 - Dec. 31, 1952

Introduction

In the past 18 months the administration of the National Cancer Institute's numerous programs has gone steadily forward. Success and failure alike have served only to sharpen the understanding of the problems involved and to increase the determination to solve them.

In the administration of its extramural programs the Institute has had the able advice of the National Advisory Cancer Council. A Cancer Control Committee has aided especially in the Institute's control activities.

The Institute's scientific staff have contributed to the general fund of cancer knowledge both by their work in the laboratories and by the communication of scientific knowledge through their publications, their participation in meetings, and their work on panels and committees. During the period under review the Institute was fortunate to secure the services of Dr. G. Burroughs Mider as Associate Director in Charge of Research. Dr. Mider reported for full-time duty July 1, 1952.

In preparation for the opening of the Clinical Center, two new branches have been established; Clinical Medicine and Surgery and Research Medicine. Cancer research activities in the fields of endocrinology, cancerigenic research, and nutrition and metabolism have been placed in the Research Medicine Branch.

The various cancer control activities have been maintained at a high level. Activities conducted with State health agencies receiving Federal aid for their official cancer programs have brought about better formulation of these programs and extension of the tenets of cancer control to all sections of the nation. The professional education programs have resulted in greater emphasis on the teaching of cancer in medical schools, an increase in the number of physicians specially trained in the skills involved in the diagnosis and treatment of cancer, and a raising of the level of cancer knowledge among practicing physicians. Considerable progress has been made in improving the cancer education of the nursing profession. Many important studies have been completed during this period and new ones undertaken. Some of these are indicated in the more detailed reports of the Control Branch.

The grant-supported research program received some increase in support during the last year. A major development in this program has been the increased emphasis on studies in the field of radiation, several of which are parts of a cooperative program with the Atomic Energy Commission. The 40 projects completed so far under the Construction Grants Program provide the nations with more and better equipped cancer research laboratories.

The Institute's relations with the American Cancer Society, the chief voluntary cancer agency operating on a national scale, have been marked by mutual understanding and cooperation. Personnel from each agency serve on committees and boards of the other, thus providing easy exchange of opinions and information on activities. Through this close liaison, overlapping of activities is largely avoided.

Improvements in the administration of the Institute's information program have brought about smoother operations, better service to the public and more effective dissemination of information on Institute activities.

The Institute's administrative costs have remained practically the same as in previous years, in the face of an ever-increasing program.

LABORATORY RESEARCH

Dr. G. Burroughs Mider is Associate Director in charge of research. The research attack on cancer progresses through steady accumulation of factual information on neoplastic diseases and other growth processes in man and experimental animals. Probably no group of individuals can yet define with reasonable certainty that one approach which offers the greatest probability of achieving effective control of clinical cancer. The research program of the National Cancer Institute must continue to be comprehensive. It must take advantage of each advance in science and technology. It must be integrated with the total effort in cancer research throughout the world but retain sufficient flexibility to make possible the shift in emphasis from one area to another as the need arises.

Biochemistry

The Laboratory of Biochemistry conducts research on basic problems of import beyond the field of neoplastic diseases and on critical areas directly concerned with cancer. Protein chemistry and metabolism receive considerable emphasis because proteins are essential components of all tissues and account for a large proportion of their functional activities. Enzymes are proteins. Progress in this difficult research has been impeded because commercial preparations of amino acids, the building blocks of protein molecules, have been available chiefly as mixtures of two different types of each amino acid which the body uses quite differently. Dr. Jesse Greenstein and his collaborators have been completely successful in separating the mixtures into their optically active parts by a cheap and practical method. This essential step should provide a great impetus to research in protein chemistry and metabolism in many laboratories throughout the world. Dr. Sandford Birnbaum, Dr. Shou-Cheng Fu, Dr. Krishnarau Rao and Dr. Greenstein are already studying the effect or specific enzymes from natural sources on the pure, optically active amino acids and have learned interesting facts concerning the effect of side chains on the metabolism of the alpha-amino group. They, with others, are separating the various tissue peptidases which break molecules containing amino acids into their constituent parts under physiological conditions. This project will ultimately provide a clue to the manner in which tissues metabolize protein materials. Three such enzymes already described were used to achieve the separation of the amino acid types. Dr. William Fones has continued his studies on the specificity of these acylases. A new enzyme active against three types of glycine peptides has the pecular property of increasing its activity on aging either in solution or in a dry (lyophilized) state.

Dr. Alton Meister and co-workers have continued their highly important and productive study of the intermediary metabolism of proteins and amino acids by normal and cancerous tissues. The animal organism can synthesize amino acids from non-nitrogenous compounds such as alpha-keto acids. This involves replacement of oxygen by a nitrogen-containing amino group. The reaction involves certain specific enzymes that act in particular cases, all of which depend on a derivative of the vitamin pyridoxine for activity. Better definition of these reactions has provided knowledge of how the amino acids enter the common pathway of biological oxidation so they may be burned and their potential energy made available for the organism. Study of bacterial metabolism has contributed importantly to progress of the group which has utilized isolated animal tissues as the major investigative tool.

Dr. Robert Greenfield devised a highly accurate constant recording apparatus for quantitative measurement of catalase activity, which he is using to study the reason why growth of a malignant tumor in a distant site diminishes catalase activity in the liver in several species, including man. A fraction rich in nucleic acids isolated from tumors of mice reduces the action of this enzyme in a reproducible fashion in intact animals but not in isolated systems. Dr. Greenfield and Dr. Vincent Price have crystallized catalase from rat liver which will allow them to compare hepatic catalase from normal and cancerous subjects.

Dr. Price has concentrated 600-fold an enzyme concerned with formation of the nucleoside bond between purines and the sugar, ribose. This reaction is an important one in metabolism of nucleic acids, essential components of all cells.

Dr. Mary Maver has demonstrated that isolated nuclei contain cathepsin, an enzyme that degrades certain proteins. She found catheptic activity higher in nuclei from cells of regenerating liver or hepatic tumors than in nuclei from normal liver. The heightened activity is accompanied by an increase in ribosenucleoprotein content. Some progress is being made in purifying cathepsin.

Dr. James Gilbert, returned from working assignments at the University of California, has been studying fatty acid metabolism. Dr. Leon Levintow, investigating the enzymatic synthesis of coenzyme A with Dr. Fritz Lipman at the Massachusetts General Hospital, found that, while the intact animal can build this material from pantothenic acid, isolated systems require a derivative of the vitamin, pantetheine. The reactions involve three distinct steps and the enzyme catalyzing the initial step was studied.

An extensive program headed by Dr. Harold Morris has added new knowledge on the way in which chemical agents produce cancer. The workers use the potent carcinogen 2-acetylaminofluorene which has the unusual property of inducing cancers in a wide variety of tissues at a distance from the portal of entry. Variations of the parent compound that might be expected to result from its alteration within the body have been synthesized and their effects studied in rats. Some modified compounds kill the experimental animals before enough time has elapsed to allow cancer production. One chemical, 2, 7-diacetyldiaminofluorene, produces multiple tumors of the intestinal tract, including the colon in rats. This has made available for study a new anatomical type of experimental cancer, the counterpart of which in man accounts for a large proportion of clinical cancers. Attempts are being made to produce such tumors in dogs with 2, 7-diacetylaminofluorene since Dr. Morris has found that 2-acetylaminofluorene itself produces primary cancers of the bladder and liver in this species. Dr. Elizabeth Weisburger and Dr. John Weisburger have found that the rats convert the original carcinogen to 12 different compounds. Dogs convert the substance similarly but relative proportions of each metabolite vary somewhat in the two species. Four of the derivatives have already been identified. Synthesis of compounds containing radioactive isotopes and study of their fate and distribution has contributed importantly to this effort. Dr. Helen Dyer has followed the course of 2-acetylaminofluorene through the body by labeling the compound with the stable isotope of nitrogen, N^{15}. Most of the label is excreted in the urine and feces within a short time of administration. A larger proportion of nonlabeled nitrogen in the original molecule, detectable by a chemical reaction, remains within the body. Some radioactive carbon and isotopic nitrogen from labeled 2-acetylaminofluorene is bound to proteins of all organs studied, regardless of the ability of the agent to elicit tumors in them. Workers at the University of Wisconsin have proposed that binding of protein by carcinogenic chemicals is an essential step in carcinogenesis with p-dimethylaminoazobenzene and 3, 4 benzpyrene. Apparently a similar phenomenon is encountered with the agent being studied at the National Cancer Institute. This approach now appears to offer a reasonable chance that the fundamental processes involved in the change from a normal to a cancerous cell will be elucidated. It also emphasizes the need for a better knowledge of protein chemistry and the chemistry of subcellular components.

Dr. Mark Woods and Dr. Dean Burk have achieved the separation of microsomes from mitochondria. They found that the microsomes have qualities not previously recognized. The soluble fraction of cells, free from particulate matter, influences the metabolism of isolated cytoplasmic bodies. The workers hope to define the contribution of the various parts of the cell to its overall metabolism, particularly as it relates to the cancerous state.

Dr. Burk and Dr. Wood have also acquired data that suggest a greater direct fixation of carbon dioxide mammalian tissues than heretofore recognized. Certain cell fractions apparently play a special role in this process. Mr. Vernon Riley, adapting flow chromatography to the separation of subcellular components, found that distinctly different fractions isolated by this process may appear indistinguishable from one another when viewed through a microscope. Mr. Riley and Dr. Kent Wight have improved and extended conventional manometric techniques that allow simultaneous recording of several variables in the course of experimentation.

Other findings of the cytochemistry group include influences of crystalline zinc-insulin on the metabolism of tumor cells, evidence for an inhibitor of cytochrome oxidase activity in cells of tumors and certain normal tissues, and data suggesting that both carbon dioxide and oxygen tensions influence lactic acid production by cells and contribute to the Pasteur effect.

Qualitative experiments carried out by Dr. Morris, and Dr. I. L. Chaikoff and Dr. Alvin Taurog of the University of California indicate that thyroxine production by normal and cancerous thyroid tissue involves the formation of the same intermediate compounds.

All work in the Laboratory of Biochemistry is strongly influenced by members of the group whose highly specialized skills are brought to bear on individual projects as the need arises. Dr. Herbert Sober continues to contribute new techniques for separation of various chemicals and new and more rigorous criteria for purity and identity of compounds. His application of chromatography and other methods of physical chemistry to various problems has been invaluable to all his colleagues. The analytical chemists under the direction of

Mr. Robert Koegel have aided the total research program by applying the most recent developments of analytical chemistry to individual problems efficiently and effectively.

Biology

Study of factors that modify the occurrence of neoplasms continues to be a major effort of the Laboratory of Biology. Dr. Howard Andervont found great variation in the susceptibility of different inbred strains to epidermal tumorigenesis induced by topical application of 20-methylcholanthrene. No correlation between the susceptibility of the skin and certain other tissues to carcinogenic action of the agent could be demonstrated nor was the ability of the agent to evoke papillomas in a given strain related necessarily to its power to evoke cancer of the skin. Dr. Duryee found that long-continued application of the powerful carcinogen 9, 10 dimethyl-1, 2 benzanthracene would not induce skin tumors in Triturus pyrrhogaster. Introduction of this agent into the limbs of the urodele caused extensive sloughing followed by regeneration of the part. The newly formed member occasionally showed abnormalities of skeletal development and some subjects developed a prominent swelling of undetermined nature in the cloacal region. Dr. Walter Heston found the ability of two carcinogenic agents, nitrogen mustard and 1, 2, 5, 6-dibenzanthracene, to induce pulmonary tumors in strain A mice was strictly additive. A comparative study of pulmonary tumors induced in 3 strains of mice and their F_1 hybrids by intravenous injection of 1, 2, 5, 6-dibenzanthracene was completed by Dr. Margaret Deringer. The degree of susceptibility of the hybrids was limited by the susceptibility of the parent strains.

Dr. Morris Barrett has found that neither long-continued direct application of 70-percent ethanol or hot water, the surgical production of polyp-like structures, nor choledochogastrostomy produces any noteworthy effect on the gastric mucosa.

The localization of primary gene action in determining susceptibility to resistance to cancer resides at least in part in organs and tissues. Dr. Heston has demonstrated that tumor development depends upon the genotype of transplanted adult or fetal pulmonary tissue rather than upon the genotype of the host. Similar data are being acquired for carcinogenesis in transplanted whole mammary glands by Dr. Richard Prehn. More general effects of gene action are also recognized since specific genes influence both body weight and incidence of pulmonary tumors. Dr. Lloyd Law finds that the thymus has a pronounced influence on the production of leukemia apart from its potential as one common site of origin of the disease. Transplantation of thymic tissue from a high leukemic strain of mice to more resistant hybrids was followed by a high incidence of leukemia in the recipients at an early age. The leukemia cells have been identified as originating in and being characteristic of the new host rather than the donor of the transplant. Filtrates and homogenates of thymic tissue do not elicit leukemia.

Dr. Law has also described a striking specific resistance in leukemia contributed by mothers of certain low leukemic strains to their offspring. Resistance is evident at sexual maturity. It increases with advancing age at parturition and eventually becomes strong enough to override genetic tendencies toward leukemia in test animals even though they represent stock with a high natural risk to the disease.

Neither Dr. Law nor Dr. Sarah Stewart has been able to demonstrate any evidence for transmittal of leukemia by a cell-free agent from mouse to mouse.

Interest continues in the agent which, transmitted from mother to offspring by suckling, influences the incidence of mammary cancer in mice. Dr. Prehn has identified the agent in spleens of deliberately infected young mice within 3 weeks after inoculation, but older subjects apparently resist propagation of the factor since it can not be demonstrated in their spleens. Mice can be infected by intracervical inoculation, by injection into the amniotic sac, or into the fetus. In each case the risk of developing mammary cancer is increased both in mother and offspring as shown by Dr. Heston. A similar but seemingly attenuated agent occurs in wild mice. Dr. Andervont has been unsuccessful in increasing its virulence by passage to mice of varying constitutions. This indicates that the thesis of latent virus infections so often postulated as major causes of cancer will be extremely difficult to demonstrate experimentally. It becomes increasingly evident that mammary tumors can develop in mice in the absence of the milk factor. Both Dr. Andervont and Dr. Heston have induced tumors of the breast by estrogenizing male mice that do not carry the agent. Dr. Andervont has also found that oral administration of 20-methylcholanthrene to mice that do not carry the milk factor but are otherwise susceptible to production of mammary cancer is followed not only by the appearance of tumors of the breast but also by leukemias that originate in the thymus.

Research on the mammary tumor inciter has taken a new and unexpected direction. Dr. Barrett and Dr. Deringer find that transplanted tumors grow more rapidly and in a higher proportion of mice that possess the agent than in those in which it is absent. These investigators see the possibility of devising a relatively simple and short test for presence or absence of the factor. Assay methods currently used require months of observation.

Dr. W. R. Duryee has found that filtrates of renal adenocarcinoma from frogs produce characteristic intracytoplasmic inclusions in single tubules as early as 6 weeks after injection. Full development of the tumor requires a much longer time and is accompanied by appearance of inclusion bodies within the nucleus and certain changes in nucleolar structure.

Dr. Ray Bryan and his colleagues have made progress towards a better method for assaying quantitatively the responses of chickens to graded doses of Rous virus. The new technique shortens the period of observation, reduces the number of birds required, and triples the number of different unknowns that may be evaluated with each test. Dissociation of lipoidal material from the active agent by enzymic techniques offers an opportunity to purify Rous virus further. The protection of Rous virus from immediate effects of X-irradiation afforded by citrate ions has been described previously. It now appears that irradiated virus undergoes slow and progressive loss of activity over a period of 24 hours. The concentration of citrate that confers maximal protection is less effective than serum. Tissue culture techniques have established the fibroblast as the cell primarily affected by Rous virus.

The ability to count nuclei and mitochondria in tissue homogenates as developed by Dr. George Hogeboom and Dr. Walter Schneider has provided them and their colleagues a means of studying carcinogenesis quantitatively. The group compared the effects of two closely related chemicals, one carcinogenic, the other noncarcinogenic, on the livers of rats. The potent agent caused a threefold increase in nuclei which could be shown to be due to proliferation of bile ducts but reduced the number of mitochondria in the hepatic parenchymal cells even though the activity of certain enzymes localized in mitochondria was increased. The livers of rats fed the noncarcinogenic compound contained approximately the same number of nuclei as did normal liver but the number of mitochondria was increased.

Dr. Wilton Earle and his colleagues have continued their study of transformation of fibroblasts of sarcoma cells in tissue culture. Eight strains of cells, originating from a single fibroblast, were grown in tissue culture. Despite their common ancestry, marked differences occurred in the ability of the separate strains to produce sarcoma when transplanted into suitable mice.

Research on biological characteristics of cancer cells has been particularly fruitful. Dr. Emma Shelton has investigated two lymphomas that arose in mice of similar age, strain, and treatment. One lymphoma remains localized, contains twice the expected number of chromosomes and amount of desoxyribonucleic acid per nucleus, no demonstrable alkaline phosphatase, and its growth stimulates mitotic activity in the host's liver. The other tumor contains both the usual number of chromosomes and concentration of desoxyribonucleic acid per nucleus and is rich in alkaline phosphatase. Further characterization of histologically similar neoplasms has great potential value in the management of clinical cancer and should represent a major effort of experimental cancer research. The field is difficult, requiring great ingenuity and perseverance. Closely related experiments by Dr. Andervont provide a firm basis for future development of this general area. He observed alteration in growth potential during serial transplantation of 36 hepatomas. The change in biological characteristics is not accompanied by systematic alterations in structural qualities of the tumors.

Dr. Andervont has found that not all primary hepatomas are transplantable within the inbred strain of origin. Nor do all tumors that are successfully propagated grow in all recipients of the same strain. This is at variance with commonly accepted genetic laws of transplantation and indicates that nongenetic influences may be limiting factors. Additional evidence of the general correctness of this view has been contributed by other members of the staff. Dr. Sarah Stewart was able to adapt strains of leukemia cells to apparently unrelated strains by injecting them into newborn mice. Residence in the very young permits the cells to grow in adult members of the same hybrid derivation and eventually they become transplantable to an inbred strain different from that of their origin. Dr. Barrett has described a permanent change in a transplantable mammary tumor which occurs when the neoplasm grows successfully in a foreign strain of mice. The change seems relatively specific with respect to the genetic constitution of the subjects used.

Dr. Glenn Algire has found that nonpigmented melanoma may be grown in albino mice, but when returned to its brown strain of origin the neoplasm always acquires the ability to form melanin pigment. He has also studied the distribution in neoplastic tissues of fluorescin proposed by others as a practical means of discriminating between certain cancers and surrounding normal tissue. All tissues studied by Dr. Algire in transparent chambers are first stained evenly by the dye which then accumulates in avascular, necrotic or cystic areas of tumors or in areas at normal tissues that have been deprived of their blood supply.

The tissue culture group have grown three tumors of different histogenesis in vitro. Each tumor produces a mass with the morphologic characteristics of sarcoma when re-implanted into mice. One of their most interesting observations relates to cells of strain L which have been grown outside the body for some years. The cells once had the capacity for growing readily as sarcomas in appropriate mice, but lost this ability. It has been found, however, that these cells will still produce neoplasms if introduced into mice of the strain from which the original explant was taken, if the recipients first receive X-irradiation.

It has generally been held that induction of an immune state by tissues requires living cells. Dr. Barrett has challenged this idea by showing that antigenic power of erythrocytes is related to their stroma. Smaller fractions produce no immunity. Dr. Prehn has provided evidence that resistance to tumor transplantation is a function of the host's economy as a whole rather than due to local tissue immunity. The experimental procedure involves transplantation of large pieces of skin between mice resistant and susceptible to growth of the appropriate tumor. Studies by Dr. Ruth Merwin with the transparent chamber reveal that vascularization is necessary for development of resistance to transplantation but not for the vulnerability to the destructive process resulting from the resistant state. Dr. Wilton R. Earle and co-workers have been attempting to grow human epidermal cells in culture, a cooperative enterprise shared with the Naval Medical Research Institute. Dr. David Campbell, California Institute of Technology, provided the workers with various antisera against human tissue components but these were not sufficiently specific in their action to remove all fibroblasts from the cultures. Antiplacental serum seems more effective at this time but it is already apparent that a long time will be required to achieve the aims of this project.

It is well known that cancer cells once extremely susceptible to the killing action of certain drugs not only acquire complete resistance to the agents but may actually depend upon them to maintain their integrity. The experimental production of such diverse qualities among leukemia cells of common origin by Dr. Law provides excellent material for studying this phenomenon which is of great clinical significance. Dr. H. E. Skipper of the Southern Research Institute is collaborating in these investigations. It now appears that the striking inhibition of formate incorporation into purines of cells that are killed by certain folic acid antagonists is reversed in dependent cells which actually increase the incorporation of formate into nucleic acids. On the other hand, sensitive cells incorporate 100 times more 8-azaquanine into their nucleic acids than do dependent ones. Differences in distribution of folic acid and the closely related citrovorum factor are not striking in two types. Combined treatment of experimental leukemias with antifolic and antipyrimidine compounds is more effective than the use of either class alone. Dr. Law postulates that a "transforming principle" accomplishes the change of sensitive to dependent cells which occurs when both types are grown together.

The past year has seen the argument advanced that the Golgi apparatus is an artifact. During this period Dr. Albert Dalton has demonstrated Golgi bodies in unstained cells and has subsequently isolated them with the aid of Dr. Schneider from tissues of the epididymis. The way is now open to study at a chemical level those differences already described by Dr. Dalton in the appearance of the Golgi apparatus among neoplasms and their tissues of histogenesis.

The ability to cut tissues as thin as 250 °A has facilitated Dr. Dalton's studies with the electron microscope. The submicroscopic lamellae that he was among the first to describe appear to be increased in hepatic cells that have become cancerous. These structures are rich in ribonucleoprotein.

Progress in cancer research is entirely dependent on better knowledge of biological reactions in general. This report includes achievements made possible by knowledge but recently acquired from the study of tissues and their functions without any thought that the factual information might ultimately be important to the study of neoplastic diseases. The gap between discovery and application is narrowing rapidly at the National Cancer Institute where communication between workers having two philosophically different attitudes is facilitated.

Our people are contributing importantly to the solid base of factual information necessary to better understanding of all growth phenomena. Dr. Clifford Grobstein is studying processes that occur in differentiating embryonic tissues of the mouse. Early developmental changes seem to be the result of intercellular relationships rather than in properties inherent within the cells. The usual development of rudiments of salivary gland, kidney, and lung proceeds satisfactorily when they are grown in culture. Their epithelial and mesenchymal elements may be separated by relatively gentle procedures. Epithelial cells from salivary gland when grown alone form unorganized sheets. Addition of connective tissue elements results in resumption of the expected morphogenetic pattern. The mesenchyme must be derived from the same organ. The kidney cultures behave somewhat differently. Separate epithelial and mesenchymal cultures from tubules characteristic of the secretory portion of the nephron. This type of change can also be evoked by the addition of epithelial rudiment of the salivary gland or by embryonic nerve tissues. None of these interesting effects has been produced with dead cells. It appears, then, that some epithelia have specific mesenchymal requirements although renal tissue is stimulated by cells other than those normally associated with it.

Dr. Earle has found that a higher rotational speed increases the growth rate of tissue cultures in roller tubes. Development of a chemically definable medium for tissue cultures is progressing. Dr. Algire has grown cells separated from the host's tissues for as long as 12 days in an apparatus attached to a mouse. His transparent chamber technique has been so modified that magnifications up to 1200 diameters are useful. Dr. Duryee and members of the staff of the Carnegie Institution of Washington have developed a new electric micromanipulator, a more efficient frozen section technique and automatic apparatus for sectioning and staining of tissues.

Biophysics

Roentgen rays damage a wide variety of tissues. Mechanisms by which total body X-irradiation kills involve easily recognizable acute changes and more subtle alterations, eventually manifested by differences in long term survival and in the incidence of those neoplasms that occur spontaneously in comparable nonirradiated subjects. The Laboratory of Biophysics is studying several of these facets intensively so a better understanding of effects of X-irradiation may be translated into more effective therapy of cancer. Total body exposure of mice to two radiations of widely different specific ionization indicated that total ionization is more important in determining the 30-day L50 dose than is the specific ionization. Dr. Egon Lorenz has extended his studies on the extraordinary protection that injection of homologous bone marrow confers on mice and guinea pigs receiving a lethal dose of X-rays. Intravascular administration of bone marrow is more effective than intraperitoneal injection, probably because the latter type of transplant undergoes considerable necrosis before it commences to regenerate. The necrotic phase is reflected by retarded regeneration of the host's marrow as compared with the prompt restoration of marrow that follows intravascular injection. The period of delay permits the development of bacteremia in mice or panleucocytopenia in both species, lethal reactions of themselves, not necessarily direct consequences of damaged erythropoiesis, although bacteremia, at least, is largely prevented by transplantation of viable blood-forming tissues.

Injections of homologous bone marrow also reduce the mortality of guinea pigs from progressive anemia induced by chronic X-irradiation from 80 to 20 percent. The only other normal tissue that consistently protects the irradiated mouse is spleen, known to possess hematopoietic function in rodents, but cells of a well differentiated reticulum cell sarcoma were also effective. Whether the protective action is caused by repopulation of damaged tissues or is due to release of some humoral factor by the transplanted cells cannot be decided now.

Although shielding of the exteriorized spleen protects mice from certain immediate consequences of total body irradiation, later effects are not necessarily modified, for long term survival is reduced equally whether or not the spleen is shielded. In C57 black mice, however, the incidence of leukemia in irradiated and shielded mice equals the 3 percent spontaneous incidence in nonirradiated controls, whereas total body X-ray treatment induces leukemia in 70 percent of intact unshielded mice of the same strain. Depression in the number of circulating leucocytes lasted much longer among the latter group, which implies that prolonged depression of leucocytes by irradiation may be an important factor in the induction of leukemia by X-rays.

Dr. J. White has described a twofold excretion of nitrogen, almost all of it as urea, after total body irradiation of rats. Shielding the spleen does not prevent excessive output of nitrogen. Rats catabolize N^{15}-labeled glycine more rapidly one hour after total body irradiation since they excrete twice as much total and labeled urea nitrogen as do comparable nonirradiated rats.

Dr. White and Dr. R. Bland Williams (Naval Medical Research Institute) have found that total body irradiation temporarily arrests mitosis in regenerating rat livers and in the epithelial cells lining the small intestine. Recovery occurs after 48 hours. Studies of protein and nucleic acid synthesis in intestinal mucosa by administering isotopically labeled compounds to irradiated subjects revealed a striking departure from the expected distribution of isotopes in nucleic acids.

Radiation-induced anemia prevents the practical use of total body irradiation as a therapeutic measure in clinical leukemias. Protection against anemia afforded by transplantation of bone marrow to leukemic guinea pigs receiving multiple doses of total body X-irradiation increased life expectancy significantly but did not result in lasting cure. Local treatment of certain transplanted tumors of mice with a single dose of X-rays was followed by a significantly higher incidence of regression when the host was exposed to an atmosphere of 95 percent oxygen than when it breathed room air during treatment. Total body irradiation did not have a similar effect under the same circumstances.

Some β-hydroxy acids are converted to the corresponding keto acids when irradiated in aqueous solutions. Citrate is converted to some unidentified compound but not to the corresponding keto acid. These molecular changes depend upon dissolved oxygen rather than on production of hydrogen peroxide.

Further study of the diagnostic and therapeutic usefulness of I^{131}, P^{32} and Au^{198} in clinical medicine has been conducted in cooperation with the Radiology Department of the University of Pennsylvania. Improved counting methods encourage further exploration of these isotopes. A small proportion of leukemic patients responded dramatically to intravenous injection of Au^{198}.

A better understanding of factors influencing the efficacy of I^{131} therapy for thyroid cancer has been attained by Dr. Seymour Wollman. He has found that a major site of impairment of iodine metabolism in transplantable thyroid tumors in mice is in their loss of ability to maintain a concentration of iodide above that in the blood, which results in an impairment of the rate of organic binding of iodide by these neoplasms. The thyroid gland of hypophysectomized mice, however, fails to incorporate iodide through some impairment of the binding mechanism, not to a lack of iodide. Dr. Wollman also found that embryonal chick thyroid tissue can concentrate iodide but acquires the ability to bind it organically during development. Thyroid cancer, then, differs importantly both from normal adult or embryonic thyroid tissue.

Changes in the concentrations of the various types of circulating leucocytes that accompany X-ray therapy of clinical cancer studied by Dr. H. Kohn in collaboration with members of the Radiation Laboratory of the University of California Medical School revealed that the patterns of change are reproducible in series of patients. Those receiving X-irradiation to the pelvis show one pattern different from that common to patients receiving therapy to the head, but each type of leucocyte responds independently. Changes in the lymphocyte count are most striking.

Cooperative research at the University of California is evaluating the relative biological effectiveness of a 70 MEV and 250 KV. X-irradiation using a wide variety of testing procedures. Another group at the Massachusetts Institute of Technology has studied the nuclear energy levels of boron isotopes, energy levels of C^{13} and O^{17} and the inelastic scattering of proton and deuteron beams from B^{10}.

Any noxious stimulus interrupts the nicely balanced economy of the individual. In some cases the more simple homeostatic mechanisms restore the equilibrium almost instantaneously. Intense stimuli may necessitate immediate major adjustments that represent obligatory means of maintaining the integrity of the organism until a sort of physiological healing permits the body to return to the type of metabolic activity which it prefers. Such drastic consequences often result in some significant change in metabolic rate, the sum total of all chemical processes in the body. An analytical approach to the study of altered metabolism seems indicated in those problems in which there is reason to believe that drastic changes in the body's chemical processes have occurred, particularly if more simple and direct methods have failed to provide the information sought. Inability to measure metabolic rates of small individual animals, particularly rats, has impeded progress in developing techniques necessary for this venture. Dr. Arnold Pratt has recently designed a practical apparatus that allows continued accurate recording of oxygen consumption, carbon dioxide elimination, and the corresponding respiratory quotient. Normal rats and guinea pigs are being studied extensively to provide a base line for the future investigation of cancer, radiation effects, and other pathologic states. The instrument is especially useful since it provides a mass spectrometer as a means of detecting abnormal metabolites in the air.

Concurrent research by Dr. White and colleagues concerns the metabolism of amino acids which have been labeled with isotopes. They have found that valine can be metabolized to a 3-carbon acid used to form glycogen. Propionate is a precursor of the intermediate formation of pyruvate. Cleavage of histidine to form glutamic acid involves removal of the α-amino nitrogen group, which appears as ammonia, and conversion of the residue through the intermediate, urocaninic acid, to glutamate. Dr. James Reid has found that histidine is an important source of carbon for synthesis of purines and contributes to the synthesis of labile methyl groups. Both conversions proceed through a formate intermediate. Some differences in the metabolism of histidine by liver and neoplasms derived therefrom are already suggested. The role of pyridoxine in transamination of keto acids to amino acids has been established in intact rats. These studies are essential to a better understanding of the functional aspects of cancerous growth which may conceivably provide a rational basis for a better approach to drug treatment of cancer.

Physico-chemical studies of biologic systems by Dr. Herbert Kahler, Dr. Murray Eden, and Dr. John Rowen are attempting to define those naturally occurring intracellular units with sufficient precision that they may be distinguished from exogenous particles such as viruses. Studies on nucleic acids by a variety of techniques indicate that they are flexible filamentous polymers of about 10°A wide and 4,000 to 7,000°A long, depending on the salt strength of the solvent. The hydrogen ion concentration of a neoplasm may decrease 0.5 pH by the parenteral injection of glucose, but a similar change does not occur in skeletal muscle. Dr. Blum, working at Princeton University, has continued his study of biologic effects of ultraviolet irradiation on arbacia eggs in respect to delay of mitosis, cytolysis, fixation, activation and dispersal of jelly membrane. He has shown that long wave ultraviolet will hemolyze erythrocytes by an oxygen-dependent reaction probably involving photosensitization by free porphyrins. The reaction is fundamentally different from the hemolysis of erythrocytes with ultraviolet rays of short length which does not require oxygen.

Chemical Pharmacology

The Laboratory of Chemical Pharmacology has accumulated more than 500 agents that produce massive necrosis in some experimental tumors. This common property is shared by such diverse substances as certain synthetic organic chemical compounds, some polysaccharides of bacterial origin, and by extracts of a wide variety of botanical products. Dr. Murray Shear and his colleagues have abandoned the search for additional agents with similar effects so that they may concentrate their efforts on determining more precisely how the common effect is elicited, and on the pharmacology and toxicology of agents already available.

The common reaction generally prolongs survival of mice bearing susceptible neoplasms but cancer cells in the depths of the tumor are damaged more severely than those immediately adjacent to the major blood vessels that supply them. This paradox is difficult to explain for one would expect that the highest concentration of the necrotizing agent would be delivered to those cells which manifest the least change if the action is directly cytotoxic. Dr. Glenn Algire has presented evidence that hypoxia consequent upon severe and prolonged hypotension with pronounced diminution of blood supply to the tumor is a major factor in the action of the necrotizing agents that he has studied. This would explain the peculiar distribution of necrosis but fails to explain why the cells of some cancers are not affected at all and why podophyllotoxin, which he used, destroys certain superficial clinical cancers on topical application.

There is reason to believe that peripheral tumor cells may be quite different in structure and in certain biological characteristics from those only a few rows centrad. Dr. Morris Belkin is studying this phase of the problem which requires some reasonably simple method of determining the vitality of individual isolated cells--a difficult task.

Cytochrome oxidase activity is reduced markedly and rapidly in tumor cells damaged by the necrotizing agents. Other enzymes associated with mitochondria are affected more severely than those enzymes that are not located in the structures that seem to be responsible for most of the oxidative processes of cellular metabolism. Normal cells do not show changes of similar relative magnitude. Dr. Vaman Waravdekar and Dr. Joseph Leiter are attempting to obtain critical evidence to decide whether these interesting alterations represent cause or effect.

The potential usefulness of bacterial polysaccharides is limited severely by their intense toxicity as determined by clinical trial some years ago. Dr. Shear has been able to reduce lethality about 50 percent for mice by giving atropine before or after administration of the agent. Progress has been made in reducing the heterogeneity of polysaccharides, a step essential to their chemical characterization. Fractionation of certain normal and neoplastic tissues has provided other necrotizing agents, presumably polysaccharides.

The potential usefulness of other tumor necrotizing agents is limited by the small margin between minimum effective dose and maximum tolerated dose that characterizes most of them. Systematic study of a series of N-heterocyclic compounds synthesized by Dr. Donald Vivian indicates that alterations of certain kinds produce predictable variation in their toxicity and antitumor activity. Dr. Leiter has found it possible to increase potency of other agents by varying substituents on basic chemical configuration. Dr. Anthony Schrecker and Dr. Jonathan Hartwell have established the chemical configuration of podophyllotoxin and its most important derivatives. A highly sensitive bio-assay procedure developed by Dr. Margaret Kelly and Dr. Leiter reveals that podophyllotoxin is inactivated rapidly when injected into animals. This drug damages blood-forming tissues.

Dr. Abraham Goldin has completed his studies of aminopterin, a useful drug in the treatment of clinical leukemias that interferes with folic acid metabolism. He found that citrovorum factor abolished the poisonous effects of aminopterin on normal cells. Concomitant administration of the two compounds to leukemia mice reduced the effectiveness of aminopterin in prolonging survival time but a massive dose of citrovorum factor given 12 to 24 hours after aminopterin treatment enhanced the effect of aminopterin. Early administration of aminopterin in the course of development of transplanted leukemia was more effective than was later administration.

Pathology

The pathologist occupies a key position in all cancer research. His skill is essential to diagnosis and proper classification of neoplasms and different morbid states that constitute other workers' tools or represent end results of their efforts. Thus a large fraction of the accomplishments listed in this report under other headings have been realized through cooperative projects in which staff members of the Laboratory of Pathology have played an important, often a critical part. The group as a whole is particularly interested in producing those types of cancer that have not yet become readily available in experimental animals, especially gastro-intestinal neoplasms and bronchogenic carcinomas, that form a large proportion of clinical cancer. Trial and error is the only practical approach at the present time and is being pursued diligently, chiefly by application of known carcinogenic agents to various sites in different species of experimental animals.

Another important function is the collection of data from the literature so it may become more readily available to investigators. Reports on transplantable and transmissible tumors of animals by Dr. Harold Stewart, Dr. Lucia Dunham and Dr. Samuel Schlyen are almost complete. A portion of the work will be published as one fascicle of the Atlas of Tumor Pathology sponsored by the National Research Council. Dr. Thelma Dunn is compiling an all-inclusive study of peripheral blood and the hematopoietic and reticuloendothelial tissues of mice and their neoplastic alterations based on review of the literature and her own extensive experience.

Dr. Willard Eyestone has continued to accumulate information on spontaneous neoplasms of dogs and cats. The histological characteristics of the lesions are being correlated with their courses, so knowledge of the natural history of cancer in these species may be more useful. The need for suitable larger experimental animals in cancer research is great. Dr. Eyestone performed 93 necropsies on captive wild animals during the past year through the good offices of the National Zoological Park.

The Laboratory of Pathology is participating in a coordinated attack on the problem of carcinoma of the uterine cervix. Epidemiologists are cooperating in seeking etiological factors in definable groups of women with high and low risks of developing the lesion so the pathologists may evaluate their influence on the occurrence of experimentally induced cervical cancer. Dr. Edwin Murphy has made the animal work practical by learning how to produce carcinoma of the cervix in mice. His research during the year has shown that this type of cancer occurs more frequently and appears earlier in mice from which the ovaries have been removed. Estrogenization seems to have little or no effect on the occurrences of the lesion but may retard its course somewhat after the cancer is fully developed. Tumors from mice that have received treatment with female sex hormones are more differentiated, containing a higher proportion of keratinized cells. The squamous cell cancers of the cervix produce mucin, hence they differ from cancers of the same type that occur in other regions of the body. Lesions in mice analogous to human in situ cancer of the cervix are being studied.

A curious lesion occurring in mice simulates the appearance of Hodgkin's disease. Further experience suggests an even closer resemblance as the result of transplantation studies by Dr. Murphy. The grafts grow little if at all in the site of inoculation but the malignant cells grow first in regional lymph nodes, then invade other lymphoid tissue including the white pulp of the spleen and occasionally metastasize to adrenals, kidneys, and liver. Serial transplantation causes a change in structure towards reticulum cell sarcoma just as "Hodgkin's sarcoma," composed chiefly of reticulum cells, develops in many victims of Hodgkin's disease.

Dr. Thelma Dunn has found in normal mice that blood from the right ventricle of the heart contains a higher concentration of leucocytes than does blood withdrawn from the left ventricle. No such difference occurs in mice with lymphatic leukemia. This is essential confirmation in another species of Dr. Bierman's excellent work in man whereby he defined the role of the lung in influencing the level of circulating white blood cells and described failure of this mechanism as one important factor in producing the hyperleucocytosis of leukemia.

Dr. Charles Congdon found that estrogen does not produce renal tumors in female hamsters although it is an effective carcinogenic agent for the kidneys of male hamsters. Tumors of the pituitary body, epididymis, and liver were also observed.

Dr. Alexander Symeonidis and Dr. Ambadas Mulay have learned that desoxycorticosterone acetate prevents the formation of hepatic tumors by the potent carcinogen p-dimethylaminoazobenzene. Dr. Mulay has described a difference in the aldolase activity of blood supplying and draining tumors. The aldolase content of different types of tumors varies. Increased concentration of serum aldolase observed in some patients with clinical cancer emphasizes the importance of this work.

Dr. Joseph Leighton's method of three-dimensional sponge matrix tissue culture is proving practical for study of both clinical and experimental cancers. It facilitates formation of organized cell aggregates and permits their study by histologic techniques. Dr. Leighton also proposes to study the effects of normal and cancerous tissues on each other by this method.

Several members of the laboratory have been studying the influence of site on the growth and structure of various transplanted tumors. Dr. Albert Hilberg observed increased bone formation by osteogenic sarcoma growing beneath the renal capsule, and Dr. Eyestone obtained a similar effect by transplanting tumors into skeletal muscle. Ultraviolet irradiation, hormone treatment, or large doses of vitamin D did not influence bone production in transplanted osteogenic tumors. Dr. Hilberg believes that essentially the same varieties of bone tumors are found in mice and in man.

Dr. Eyestone has completed his histological studies of the common reaction of mice, rats, rabbits, and dogs to podophyllin compounds, of which Beta peltatin is the most active. These tumor-necrotizing agents seem to arrest cell division primarily. Effects on lymph nodes are observable within 15 minutes after subcutaneous injection. Recovery requires 6 days. Hematopoietic tissues, intestinal epithelium, gonads, and the thymus are the most susceptible tissues. These same tissues are also those most readily damaged by antifolic and nitrogen mustard drugs that are useful in treating certain forms of clinical cancer.

Dr. Eli Nadel and staff members of the National Microbiological Institute have found that deliberate infection of leukemic mice with malarial parasites increases their life expectancy. An antimalarial drug and the antifolic agent, amethopterin, both prolong the lives of leukemic mice but combined treatment is more effective than is doubling the dose of either drug alone. Dr. Nadel also discovered that Kurloff cells appear in excessive numbers in the spleens of guinea pigs treated with estrogenic substance. He studied the decrease in alkaline phosphatase that accompanies the development of ascorbic acid deficiency and found that large quantities of ascorbic acid were necessary for adrenal corticoid excretion in scorbutic guinea pigs.

The technology section under Mr. Albert Kessel's able direction not only prepared histological material from more than 106,000 specimens submitted from all laboratories of the Institute but found time to improve existing methods and devise new ones.

Experimental Oncology

The Laboratory of Experimental Oncology under the able direction of Dr. Michael Shimkin operates in conjunction with the University of California School of Medicine and the San Francisco Department of Public Health.

The clinical research group has continued to exercise remarkable ingenuity in studying problems of cancer in man. Dr. Howard Bierman, Dr. K. H. Kelly, Dr. Laurens White and Dr. R. L. Byron have extended the use of intravascular catheterization to the thoracic duct, finding that the lymph does not contribute enough lymphocytes to the blood stream to influence materially the hyperleucocytosis that often accompanies leukemia. Further experiments on the physiological dynamics of circulating leucocytes in man have shown that histamine produces different effects on the concentrations of white blood cells in the 3 major types of leukemia. Epinephrine causes release of leucocytes trapped in the pulmonary circuit while pilocarpine is followed by venous leucocytosis.

Transfusion of whole blood or plasma from patients with idiopathic thrombocytopenic purpura to patients with cancer caused precipitate fall in blood platelets that lasted for 24 to 96 hours. The venous blood was affected much more rapidly than was the arterial, indicating that the platelets were probably removed while circulating through capillaries.

Dr. Nicholas Petrakis is developing a microspectrophotometric technique which he used to study the desoxyribonucleic acid content of individual nuclei. Patients with relatively acute leukemias generally had a higher proportion of cells with increased content of DNA than did those suffering from more chronic leukemias. Dr. Petrakis also found higher pressures in the bone marrow of leukemic patients than in nonleukemic subjects. Greatest pressures were recorded in those with acute leukemias. Related studies in which Dr. Serafeim Masouredis also participated suggest an increased rate of blood flow in leukemic marrow. The technique involved the measurement of clearance rates of radioactive iodine injected into the part to be studied.

Dr. Bierman and colleagues have found that the vascular bed about primary cancers and their metastases is often increased and distorted as revealed by roentgenograms made after introduction of radiopaque material through intravascular catheters. Primary lesions of the lung injected through the pulmonary artery fail to reveal increased vascularity, however, and the vascular bed of the liver is actually reduced when the organ is involved in Hodgkin's disease. Blood vessels about cancers seldom respond to epinephrine, norepinephrine or histamine as do blood vessels in noncancerous tissues. The group has developed a method for sampling blood in the portal vein through introduction of hypodermic needles. Portal venograms have been made on several patients in collaboration with Dr. Steinbach, University of California.

Many patients with cancer, particularly leukemia, have increased plasma volumes. This observation has led to the use of red blood cells rather than whole blood in transfusions, resulting in diminished occurrence of post-transfusion hemorrhagic complications.

The use of a variety of chemicals as therapeutic agents against cancer has not achieved any noteworthy success. One compound, 1, 4-dimethylsulfonoxybutane, however, that selectively reduces granulocytes, produced satisfactory responses in patients with chronic myelocytic leukemia. Dr. Shimkin is studying the natural courses of several anatomical types of cancer. This information is essential to better evaluation of all forms of therapy of cancer. An excellent study of mammary cancer has already been published. Those on childhood leukemias and myelogenous leukemias are complete.

Dr. Leo Melcher and Dr. Masouredis used immunochemical techniques to show that mitochondrial proteins seem to be related to serum beta globulins. They are also investigating the use of radioiodinated antibodies as indicators for the presence or absence of antigenic proteins in intact animals. This interesting approach has been successful when the experimental system included foreign proteins such as ectromelia or ovalbumin.

Certain differences in depolymerizing enzymes obtained from a tumor and the blood serum of mice have been described by Dr. Joseph Shack. He reports little difference in the nucleic acids derived from calf thymus or mouse lymphoma with respect to several physico-chemical qualities.

Dr. Bernard Shacter reported that plasma sulfhydril levels decrease with progressive growth of a rat lymphoma and rise when the tumor regresses.

It is a source of real regret that circumstances beyond control of the National Cancer Institute require termination of clinical investigation at the Laboratory of Experimental Oncology on June 30, 1953. The unique approaches and amazing productivity of the clinical research team have stimulated much research throughout the country. Dr. Bierman, who must be given great credit for these accomplishments, has elected to remain in California rather than join the staff at Bethesda.

Research Medicine

A Research Medicine Branch, Dr. Ray Hertz, Chief, was created late in the year to anticipate the increase in clinical facilities that will occur in 1953. Sections on endocrinology, environmental cancer, and nutrition and metabolism are currently operating. Dr. W. C. Hueper's report on environmental cancer activities is presented in the section on Cancer Control Programs since the group has been under the administrative direction of the Associate Director in Charge of Research for only a brief period. The Nutrition and Metabolism Section is too recently formed to have achieved results.

The endocrinologists report progress in several directions through the combined efforts of Dr. Hertz, Dr. Monte Greer, Dr. Stanley Green, Dr. George Fisher, and Mr. William Tullner. In comprehensive studies of the role that hormones play in the etiology, course, and treatment of clinical cancer, emphasis has been placed on studies of carcinomas of the breast, prostate, and uterine cervix. Additional data on the effects of massive estrogen therapy on the course of mammary cancer have been acquired as part of the program of the Committee on Therapeutic Trials of the American Medical Association. Intravenous progesterone therapy is now practical and seems to be tolerated well by patients. A compound has been found which is more than 5 times as active as progesterone and has the distinct advantage of being active when given by mouth. These two new developments have many implications for the better management of gynecological disorders in general, including cancer. Biological antagonism between pregnandiol and progesterone, demonstrated by deciduoma reaction, was not detected in experiments with rabbits using progestational proliferation, a more critical end point. Daily injections of progesterone restore the reproductive cycle of rats in which persistent estrus has been produced by injury of the hypothalamus.

Previous observations that certain antagonists of purine metabolism will prevent tissue growth responses to estrogen have been extended to monkeys, indicating effective interference with peripheral action of the hormone.

Development of research in the direct action of hormones on tissues is greatly to be encouraged. It probably requires a closer study of the relation of these potent agents to metabolic processes. Dr. Hertz and his colleagues have been unable to demonstrate that glyconeogenesis stimulated by cortisone depends on the hepatic content of B-complex vitamins. The rates at which atrophic changes develop in several target organs following deprivation of hormonal stimulation are relatively constant. They are not affected by various experimental procedures including vitamin B-complex deficiency, administration of antagonistic steroids, thyroidectomy, or thyroxine treatment.

Hydatidiform mole is a pathological consequence of some pregnancies. It may be the precursor of highly malignant choriocarcinoma. It now appears that urine from patients with hydatidiform mole contains no histidine which is usually excreted in the urine of pregnant women. A test that may become valuable in differential diagnosis may result from this observation. Collaborative work with the Tissue Culture Section indicates that tissue from hydatidiform moles may produce chorionic gonadotrophin for as long as 16 months. No correlation exists between degree of cellular dedifferentiation and hormonal output. The presence of chorionic gonadotrophin in the spinal fluid has been considered diagnostic of choriocarcinoma, but Dr. Hertz and Dr. Robert Barter of George Washington University have found this hormone in the spinal fluid of 7 healthy pregnant women.

The suppressant action of rape seed oil on adrenal function proved to be too weak for practical purposes. A new chemical, however, does depress adrenal cortical activity in the rat and is more easily synthesized than amphenone.

As a result of the consistent failure to induce prostatic carcinoma in dogs or monkeys by prolonged administration of testosterone propionate, the investigators have resorted to diversion of the venous blood from the testis to the prostate through surgical operation. Results of this interesting study are not yet available.

The group continues to study people whose somatic development has been abnormal as the result of endocrine stimulation. The experience is extremely valuable in determining both the action of hormones on various tissues and the interrelations of endocrine glands.

Clinical Medicine and Surgery

The Clinical Medicine and Surgery Branch has recently been activated with Dr. Robert R. Smith, Chief Surgeon NCI, acting as chief. Sections on surgery, medicine, and clinical chemotherapy will be staffed largely by members of the Institute currently being trained in Public Health Service or university hospitals. Dr. Smith plans to study the effect of cigarette smoking in animals by creating a bronchostome. Dr. William Butler, at the Johns Hopkins Hospital, is perfecting his method for perfusing prostate glands from dogs and other animals which will allow him to study the physiology of this organ so often affected by cancer. Dr. Ezra Greenspan, working with the staff of the Mount Sinai Hospital in New York, has found that the level of serum mucoprotein is a useful adjunct in the differential diagnosis of obstructive and hepatogenous jaundice. Correlations between the ratio of serum protein-bound polysaccharide to mucoprotein and other plasma protein fractions are being sought.

Dr. Virginia Downing has collaborated with Dr. Sydney Farber in studying the therapeutic use of a new series of triazine compounds developed at the Boston Children's Hospital. Dr. James Holland, working with Dr. Alfred Gellhorn at the Francis Delafield Hospital in New York, has gained valuable experience in clinical chemotherapy. The usefulness in New York of 1,4-dimethylsulfonoxybutane in myelocytic leukemias parallels the experience of Dr. Shimkin's group with the same compound. Dr. Holland has also reported some quantitative differences in the response of patients with metastatic mammary cancer to dihydrotestosterone as compared with testosterone propionate.

Dr. Smith has participated actively in the surgical services of several Washington hospitals during the year. He and Dr. Hertz have also contributed to teaching efforts of the local medical schools.

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The opening of the Clinical Center will provide greater opportunities for the investigation of clinical cancer. Experimentalists have much to contribute to this effort. Facts obtained from the study of animals may be affirmed in man and problems originating in the clinic may be taken to the laboratory for further analysis. Both approaches are necessary; both are fundamental. It becomes increasingly clear that direct study of cancer in either man or animal is seriously impeded by gaps in our knowledge of basic biology, biochemistry and biophysics. A large proportion of our program must continue to be focused on these critical areas.

GRANT-SUPPORTED RESEARCH

The Research Grants Branch, Dr. R. G. Meader, Chief, has the following duties and responsibilities:

1. To administer funds appropriated by Congress for
   - (a) The support of basic and applied research in cancer and closely related fields carried on in non-Federal institutions.
   - (b) The granting of fellowships to qualified investigators or students for training and special research in these fields.
   - (c) The construction of facilities in non-Federal institutions for the housing of research and training activities in cancer.
2. To provide the Surgeon General, the National Advisory Cancer Council, and other reviewing panels with adequate information upon which to reach decisions as to allocation of the funds designated for the above purpose.
3. To stimulate and promote cancer research and the diffusion of knowledge thereon.

Administration of Funds Provided by the Congress

In administering the grant-in-aid funds, the Branch is assisted by the Division of Research Grants of the National Institutes of Health, which handles audit and fiscal control of all allocated cancer grant funds subject to direction of the Branch Chief.

Research Grants

Three 3-day meetings of the National Advisory Cancer Council were held during the fiscal year (October 1951, February and June 1952). At these meetings there were presented 520 applications totalling $6,553,711, of which 431 totalling $4,830,997 had beginning dates in the 1952 fiscal year. Of the 520 applications reviewed, the Council recommended and the Surgeon General approved 412 for $4,353,190. Since of the approved projects only those with a beginning date within the fiscal year are paid from 1952 funds, 325 grants totalling $3,165,058 were paid.

The paid grants were to applicants in 113 institutions in 37 States, the District of Columbia, Puerto Rico, and 6 foreign countries. Some were extensions or replacements of grants previously active.

As of July 31, 1952 (date of the last active list), there were 416 active cancer research grants amounting to $4,672,431 at 158 institutions in 38 States, the District of Columbia, Puerto Rico, and 7 foreign countries. These grants support both clinical and fundamental research related to cancer.

Construction Grants

Since no funds were provided in the 1952 Appropriation Act for this purpose, no new construction grants were awarded during the year although 22 formal applications totalling $6,384,845 are on hand. In addition there are supplementary requests for more than $9,000,000 and 38 institutions have expressed their intent to file application if money is made available. Construction on those projects for which funds had been granted previously proceeded during the year. By the end of December 1952, construction on 40 projects had been completed and the facilities were in use. Construction had been started on fourteen others, while for the remaining one, plans are prepared and contracts are expected to be awarded soon. Of the money appropriated for fiscal year 1952 to liquidate prior years' contract authority, $1,801,950 had been paid by December 31, 1952.

Research Fellowships

During the 1952 fiscal year 260 applications for cancer fellowships were received in the amount of approximately $807,040. The Central Qualification Board passed 254 as meeting minimum requirements and referred them to the Cancer Specialty Board which was able to recommend only 161 grants for $499,763 to the Surgeon General for approval. That relatively few of these were so recommended was due for the most part to the limitation of funds.

The grants recommended were, by classes, as follows:

Pre-doctoral	98	$231,708
Post-doctoral	58	247,030
Special	5	21,025

These fellowships will aid training and research in 49 institutions, located in 22 States, in the District of Columbia, and 4 foreign countries.

As of December 31, 1952, there were 112 holders of National Cancer Institute fellowships on active duty or to go on active duty within six months.

Purpose of the Cancer Grants Program

The purpose of the grants programs is to aid in solving the following problems:

1. The problem of carcinogenesis, i.e., what are the cellular changes involved in the transformation of the normal cell to the cancer cell and how are these brought about.

2. The problem of tumor development and of host-tumor relationship, i.e., what are the factors controlling the development of cancer and how are these related to the host.

3. The problem of diagnosis, i.e., what means are there for discovering the presence of a tumor in the host.

4. The problem of prevention and therapy, i.e., what means are there for (a) the prevention of carcinogenesis, (b) the prevention of tumor development if carcinogenesis has occurred,

(c) the eradication of the lesion, or reversal of the carcinogenetic process.

The grant-in-aid program of the National Cancer Institute is devoted to research on all these problems with particular interest in the eventual and immediate application to cancer in the human. In supporting fundamental research in which the relationship to cancer may not be immediately evident to some observers, the advisers to the Surgeon General have in mind that most of the significant advances in science, even at the level of treatment of diseases in man, have been made possible largely through a reserve of fundamental information. It must also be remembered that since we do not as yet know the one road that should be followed to reach the ultimate goal of control and prevention of cancer, we must offer support to those competent workers concerned with numerous avenues of the problem even when the connection with cancer is not immediately obvious to every one. These avenues of research and the philosophy guiding the interpretation of their relationship to the ultimate goal are very excellently discussed in the introduction to the Sixth Annual Report of the National Research Council's Committee on Growth, "Trends in Cancer Research," and need no further elaboration here. Rather, a few examples taken from the work of some of the grantees will be given to illustrate some of the approaches being made in the attack on the problems given above. These are selected from among the more than 400 investigations supported by grants from the National Cancer Institute.

Projects Relative to Carcinogenesis

In an attempt to understand how certain chemical compounds cause cancer when administered to an animal, Dr. Charles Heidelberger has been carrying out extensive studies at the University of Wisconsin on just what happens to some of these compounds in the body. He has synthesized a number of these carcinogenic compounds containing isotopically-labeled atoms in order that he may learn how the material is distributed throughout the body and into what other compounds it is converted. In this way additional information relative to the problem of the mechanism of the initiation of cancer will be obtained.

Projects Relative to Tumor Development and the Host-Tumor Relationship

Dr. George B. Brown at the Memorial Center for Cancer and Allied Diseases is studying nucleic acids in relation to cancer. This problem is especially important since the evidence has been accumulating that these chemical components of the cell may be especially concerned with the regulation of the formation of protein, and therefore with the growth of cancer cells. Dr. Brown has been studying the intricate details, predominantly from a chemical standpoint and employing isotopically-labeled compounds, as to how the nucleic acids are formed and what happens to them in both normal and cancer tissues. In addition to the very important fundamental information obtained in these studies and on the basis of these data, Dr. Brown has been able to formulate one rational approach to the treatment of cancer with chemical materials. He and his collaborators have synthesized various compounds which are similar in structure to those compounds found to lie on the normal pathway followed in the course of metabolism concerned with nucleic acids; these synthesized compounds are similar enough to the normally occurring compounds that they become involved in the usual chemical reactions, but are different enough to cause a blocking of the reactions at certain points along the way. Thus, many of these newly made compounds, known as anti-metabolites, have been effective in causing a partial regression of tumors. The search for a drug that will be an effective treatment for cancer is thus removed from a random type of selection and is put on a more rational basis.

Projects Relative to Diagnosis

Dr. Claude R. Hitchcock at the University of Minnesota is attempting to improve the diagnosis of cancer of the stomach, a type of cancer in which there is great need for early and accurate diagnosis since this kind of tumor is particularly prone to advance to an inoperable stage before diagnosis is made by present methods. Dr. Hitchcock is continuing a study initiated by Dr. O. H. Wangensteen and Dr. David State to find easily determined physiological and pathological conditions which may be correlated significantly with gastric cancer and which may indicate its presence earlier than it can be diagnosed by other means. Among these potential precursors which may be associated with or precede frank and recognizable gastric cancer are decreased gastric acidity, pernicious anemia, the presence of gastric polyps, and other disturbances of the stomach lining. This is a long term study and the final results will not be available for several more years. Preliminary experience suggests, however, that the occurrence of gastric cancer is related to the occurrence of gastric polyps and that both are related to a decreased acid secretion of the stomach lining. If this proves to be the case, it may be that the reduced or lost ability of the stomach lining to produce acid will be a means of selecting those individuals who should be carefully studied for a possibly existing gastric cancer or who should be followed by careful periodic examinations to discover in its early state a gastric cancer.

Projects Relative to Therapy

Radiation has been looked to for further improvement as a means for controlling cancer. The areas where improvement is looked for are (1) localization and better knowledge of the amount of energy required to destroy a tumor, (2) some means of delivering a more effective dose to the tumor with less damage to skin and intervening or adjacent tissues, (3) means of altering tumor tissues to become more sensitive to radiation and means of altering or protecting normal tissues so that they become less readily affected, (4) means for counteracting the damaging effects of radiation to prevent the undesirable early and later sequelae of exposure, such as fatigue, nausea, vomiting, diarrhea, decreased formation of blood elements, bacteremia, etc. All of these aims are being sought in projects supported by grants. For the purpose of this report, however, it may be of most interest to concentrate on those which are concerned with delivery of more effective dosage to deeply situated tumors or to tumors which appear resistant to conventional energy levels.

The depth of penetration of X-rays, electrons, etc., is roughly proportional to their energy as well as related to other characteristics of the rays or particles and the character of the tissue penetrated. With recently developed instruments, ionizing radiations ranging upward from 1 million electron volts are becoming available for clinical use. To find out whether the therapeutic results induced by use of high energy radiation from such instruments are significantly better than those obtained with conventional sources of lower energy, the National Cancer Institute has made grants to permit evaluation. Another purpose of these grants is to permit extension of research on the nature of the biological effects of high energy radiation on cancerous and normal cells and tissues. An example is the grant to Swedish Hospital in Seattle to provide for part of the cost of purchases and housing of a 2-MEV instrument. For a number of years Dr. Simeon Cantril and his associates have carried out careful therapeutic programs in cancer using radiation of up to nearly 1 MEV. The new instrument will permit evaluation of the effectiveness of still higher energies of radiation in comparison with those previously used and with the studies of others who will be using similar or more powerful radiation beams.

Chemotherapy

Although surgery and radiation remain our best means of therapy of cancer, and advances in their use have noticeably affected and will probably continue to affect the five-year survival rate of patients thus treated, the limitations in these approaches are well recognized. Control of cancer through natural or synthetic chemical products is being vigorously attempted. Thus far no agents have been found which are uniformly effective in the sense of being a cure or which can be used alone in patients for whom surgery and radiation offer promise. But there are agents which, alone or in combination with surgery or radiation, have a palliative action. The palliation in rare instances may be quite long lasting but more often is brief. The finding of agents with some effectiveness in control of cancer encourages the search for more effective compounds and suggests some rationale for the selection of candidate compounds for evaluation.

At the College of Physicians and Surgeons of Columbia University, Dr. Alfred Gellhorn is studying the mechanism of action of chemotherapeutic agents against tumors. He is seeking (1) to define precisely the cellular content of various biochemical entities, e.g., nucleic acids, enzymes, and coenzymes which may be presumed to be affected by a chemotherapeutic agent, (2) to investigate the changes, if any, under the influence of the agent, (3) to localize the precise site of action of the agent in affecting these biochemical entities, and (4) to determine the metabolic fate and the effective cellular concentration of the chemotherapeutic agent *in vitro*.

In the study of an agent, 8-azaguanine, it was found that the reason it had an inhibitory effect on the growth of four types of animal tumors and no effect on normal tissues or three other types of tumors was due to the presence in normal tissues and resistant tumors of sufficient quantities of an enzyme that could convert the toxic drug into a harmless compound. The tumors inhibited by the agent lacked this enzyme in sufficient quantity to protect their cells. It was found in tissue culture studies by Dr. Margaret Murray that cells of a human malignant brain tumor (glioblastoma multiforme) are inhibited by the drug. Dr. Gellhorn also found that normal human brain tissue has the protective detoxifying enzyme whereas it seems to be lacking in the tumor tissue. The way was thus opened for clinical trial of the drug. This is now going forward but final results are not yet available. Whether these prove successful or not, the studies will have indicated one rational approach to the selection of chemotherapeutic agents which may eventually be able to control the growth of tumors with little or no injury to normal cells.

PROVISION OF INFORMATION TO THE SURGEON GENERAL AND ADVISORY GROUPS

In this operation the Research Grants Branch has assistance from the Project Review Officer and the Study Sections of the Division of Research

Grants. That Division receives and processes all applications for cancer research grants. Before these are presented to the National Advisory Cancer Council for final review and recommendation to the Surgeon General, most of them are submitted to one of the study sections for technical review and evaluation. Because of the complexity of the cancer problem and the diversity of approaches called for in its study, no fewer than fifteen of the twenty-one study sections and special committees are called upon for aid to the National Advisory Cancer Council in advising the Surgeon General as to the merits of particular proposals.

Applications for the review of which no study section is deemed appropriate are made ready by the Branch for review by the National Advisory Cancer Council.

All types of research grant applications are submitted by the Branch staff to the National Advisory Cancer Council at three regular Council meetings each year. When special problems are associated with a particular application, arrangements are made by the Branch for visits to the applicant by Council staff or members, or Council Subcommittee meetings with Study Section members and special consultants. Such meetings were arranged to consider grants in the field of therapy by supervoltage radiation, studies of the biological effects of penetrating ionizing radiations in subhuman primates, and clinical evaluation of chemotherapeutic agents for human cancer.

Fellowship applications are dealt with through the Office of Fellowships of the Division of Research Grants. After screening by the Central Qualification Board and the Cancer Specialty Board, those passed by the latter are recommended to the Surgeon General for approval. The Chief of the Branch serves as a member of these two Boards.

An analytical classification of cancer research activities was devised by Dr. H. W. Chalkley, Assistant Chief of Research Grants Branch. Using a standard questionnaire, each applicant classified his own research project by checking appropriate descriptive designations for the facets of the cancer problem, the research methods, and the anatomical site of the cancer (organ or tissue) he is studying. This information is transferred to a punch "keysort" card. By this method there is available ready cross-reference for all items included in the classification as well as for certain additional information such as grant terms and funds and the geographical location of the investigator. This system has proved especially helpful in obtaining information for the National Advisory Cancer Council, Study Sections, the Surgeon General and his staff, and the Bureau of the Budget. Its most important function, however, will be to ascertain trends in cancer research.

STIMULATION AND PROMOTION OF CANCER RESEARCH AND THE DIFFUSION OF KNOWLEDGE

In two areas the National Advisory Cancer Council has suggested the stimulation of special research efforts - these are in the areas of gastrointestinal cancer and of radiation. A Committee on Gastrointestinal Cancer was set up several years ago directly upon recommendation of the Council. The Committee and the Council through the National Cancer Institute have sponsored five national conferences on this problem for the exchange of new research knowledge and for the development of new ideas. The Fifth National Conference on Gastrointestinal Cancer was held in Cincinnati on March 3, 4, and 5 of 1952.

The Committee has also arranged for a cooperative study to determine the truth of the often-quoted statement: "Of people who die with gastro cancer unoperated, in 26% of the cases the lesion is confined to the stomach or to the stomach and the immediately adjacent lymph nodes." The Veterans Administration has been interested in collaborating in this study. The efforts of the Committee have been largely responsible for the increase in research on gastrointestinal cancer that has become evident in recent years.

In the area of radiation the Council has recommended to the Surgeon General that efforts be especially encouraged to (1) learn more about the mechanisms by which radiation energy affects various types of normal and malignant cells, as well as the total organism, (2) evaluate the relative therapeutic effectiveness and advantages of different levels of radiation energies, (3) study means for potentiating the effects of radiation on malignant cells and for protecting normal cells or minimizing the damage to them, (4) discover means for preventing or counteracting the deleterious effects of radiation on the whole organism as exhibited in the symptoms of radiation sickness. In carrying out these recommendations, the Branch staff has maintained continuing liaison with the Atomic Energy Commission and other agencies with similar interests to avoid undesirable duplication or overlapping of effort. Activities under item (2) have been described above under "Therapy." The other three aims are being promoted in part through studies of the effects of ionizing radiations in subhuman primates. These studies are being stimulated and guided by the Committee on Radiation Studies established by the Division of Research Grants on the suggestion of the National Cancer Institute. The Committee serves all grant programs of the National Institutes of Health that have an interest in this field and also advises the Atomic Energy Commission on the primate studies which are closely coordinated with those of the National Institutes of Health.

CANCER CONTROL PROGRAMS

The Cancer Control Branch, under the direction of Dr. R. F. Kaiser, has continued to operate its many activities through the mechanisms of extramural grant programs, operation of field studies, direct assistance and consultation to numerous organizations interested in cancer control.

Extramural grant activities include five programs: cancer training grants, cancer control project grants, grants to State Health Departments for cancer control purposes, clinical traineeship awards, and radium loans.

Cancer Training Grants

The cancer training grant program provides funds in amounts up to $25,000 for approved 4-year medical and osteopathic schools, and up to $5,000 for approved 4-year dental and 2-year medical schools for the improvement of cancer teaching to undergraduate students. July 1, 1952, marked the fifth anniversary of the initiation of this program which has expanded to the point where 79 medical, 40 dental, and 6 schools of osteopathy participated in the grant activities during the past 18 months.

The program is conducted on a project basis with each school making application annually for grant support. The applications are processed by the Cancer Control Branch and presented for technical review and evaluation to the

Cancer Control Committee, which serves as a study section, and the National Advisory Cancer Council for final recommendation.

The diagnostic acumen of undergraduate medical students has been sharpened through the cancer teaching program as evidenced by the "cancer learning test," an evaluation procedure carried out annually to check the students' knowledge of cancer. The results of this test in 1952 showed that the cancer knowledge of the students in each year of medical school had significantly increased over that possessed by students in the corresponding year at the beginning of the program. In addition, the program has been responsible for establishing within the schools a focus of cancer interest, centered in a Cancer Coordinator appointed in each school. This development has served not only to increase the interest of the faculties in cancer teaching but in cancer research and other matters relating to the cancer problem as well. The coordinators have formed an effective association which meets annually to review and discuss their cancer teaching programs. During this reporting period, meetings were held in Cincinnati in October 1951 and in Boston in September 1952. The branch staff has participated directly in these meetings through the presentation of papers and through advisory and consultation services to individual coordinators. Additional liaison and consultation services have been maintained through field visits to a majority of the schools. Staff members have published a number of papers on the teaching program.

Cancer Control Project Grants

The Cancer Control Project program is concerned with field studies relating to the prevention, discovery, diagnosis, and treatment of cancer, and the promotion of the useful application of the results of research and other activities with a view of the development and prompt, widespread use of the most effective methods of prevention, diagnosis and treatment of cancer.

Through the mechanism of cancer control project grants, working arrangements have been entered into with a large number of organizations and institutions throughout the country. One hundred and forty projects were reviewed by the Cancer Control Committee and the National Advisory Cancer Council, of which 85 were recommended for approval by the Council. Of these, 20 awards were for studies which show some promise of contributing to knowledge of cancer prevention; 8 were concerned with studies on the early discovery of cancer; 22 dealt with cancer diagnosis; 7 were in the area of cancer therapy; 25 were in the field of professional and lay educational activities; and 3 were concerned with cancer services.

Specific accomplishments include the demonstration of the multicentric origin of lung cancer by Dr. Edward J. McGrath at the University of Cincinnati School of Medicine; the development and production of an improved X-ray seriolograph by Dr. Armand E. Brodeur and other staff members at the St. Louis University School of Medicine, which will enhance X-ray diagnostic procedures for some carcinomas; an evaluation of reported cancer diagnostic tests at the University of Tennessee, University of Kansas, University of Washington, University of Alabama, and Tufts Medical School; extension of the use of the cytologic test as a diagnostic aid in cervical and uterine cancer; production with the American Cancer Society of a professional cancer teaching file, "Uterine Cancer"; production jointly with the New York State Department of Health of a cancer control manual; conduct of the Second National Cancer Conference in Cincinnati, Ohio, on March 3-5, 1952, in collaboration with the

American Cancer Society and the American Association for Cancer Research. This conference was attended by a capacity audience of over 1,400 scientists, clinicians, and other professional individuals interested in the cancer problem. The branch staff made a significant contribution in the organization of the conference program and the establishment of an inter-organizational group for the review and evaluation of reported cancer cures.

State-Aid Program

The State-aid program provides grants to the official State and Territorial health agencies to conduct cancer control activities within their jurisdictions. Funds are granted on a formula basis which takes into account population need, population density, cancer mortality, and extent of financial need. Each State matches every two dollars of the Federal funds with one dollar derived from State sources.

Activities supported in the States by means of these funds include cancer registers, cancer reporting systems, statistical services, lay education programs, professional education programs for physicians, nurses, dentists, pharmacists, and school children, histopathologic services, biopsy services, cytology services, nursing services, cancer clinics and detection centers, cancer hospitals, medical consultation services, medical social services, advanced care services, and diagnostic hospitalization service. In general, all of these services were initiated or expanded in varying degrees by various State health agencies during the reporting period. An important gain has been an increase in the number of cancer diagnostic and treatment clinics, either through the establishment of a new facility or the conversion of a detection center to a cancer clinic. An additional number of cancer coordinating councils has been established at the State level. Improvement in the respective State programs has been accomplished under the direction of Dr. Noka B. Hon, through the provision of consultation service--medical, nursing and statistical--to State and local health departments and regional Public Health Service offices. Practically every State and regional office has been visited at least once, either in connection with program reviews or consultation services of one type or another during the reporting period. A program guide handbook, developed by the branch for regional Public Health Service offices, activated in July 1952 has definitely strengthened the consultation services provided through this program. In like manner, the semiannual State Cancer Activity Report Form, developed by the branch during the year and placed in use in December 1952, will make it possible to provide an improved type of consultation service as well as a better understanding on the part of the States of their own programs.

Traineeships

The largest number of trainees in the history of the clinical traineeship program were supported during the past 18 months, 215 physicians in 62 institutions throughout the country. Eight new institutions were added during this period. As of December 31, 1952, there were 125 trainees on active duty. Requests for support during the past year increased markedly and were considerably in excess of the number of individuals who could be supported. These trainees form the nucleus around which additional cancer clinics and various cancer services are built.

Radium Loans

The radium loan program in operation since 1939 was continued on an annual contract basis with radium being provided to qualified radiologists in approved hospitals. Practically all of the radium available for loan, 8,507.5 milligrams, has been used by 54 institutions during the past 18 months. A survey has been initiated to determine the actual utilization of the radium on loan, but analysis of the data remains to be completed.

Field Investigations

The search for new diagnostic tools, under the direction of Dr. John E. Dunn, has continued with the interest of the branch primarily centered in the evaluation and development of general diagnostic tests for cancer and the study of the vaginal cytology technique for uterine cancer case-finding. Under this program direct liaison, consultation, and statistical services have been maintained by staff members with groups in five university centers where evaluation of reported cancer tests has been accomplished. By and large, the evaluation phase of this activity has been completed on the tests at hand and, until new tests come along, activities are shifting to the development of diagnostic tests. A large number of papers on the current evaluation work have been prepared by staff members and members of these university groups. These are being assembled for publication.

The Clinical Trials Unit operated by the branch at the University of Washington Medical School, Seattle, has continued its work on diagnostic tests and development although reduced in force since July 1952, preparatory to bringing the group to the Clinical Center when laboratory space becomes available.

During the early part of this reporting period the branch spent a considerable amount of effort in organizing, assembling, and training the staff for the vaginal cytology case-finding project which was placed in operation at the University of Tennessee Medical School, Memphis, in July 1952. The project is designed to determine the usefulness of cytology as a cancer case-finding procedure. It is anticipated that all women over 20 years of age in Memphis and Shelby County, Tennessee, will be screened in the study. In order to have baseline data for the analysis of the results of this screening program, a morbidity study covering the calendar years 1950-51 was carried out in collaboration with the Biometrics Section. The screening program has been gaining acceptance and participation by both the public and physicians of the area, and it is expected that the activity will operate at full capacity during the next year.

During the reporting period a number of publications, manuscripts and presentations on cytology were prepared. Staff members have actively participated in the preliminary work of organizing two separate cytology societies.

In October 1952 the Field Investigations Section was made a part of the Field Studies Section of the branch.

Cancerigenic Studies

The Cancerigenic Studies Section under the direction of Dr. W. C. Hueper is concerned with the relation of environmental factors to cancer. The activities included the planning of and collaboration in occupational cancer surveys, consultation services and laboratory research. Technical assistance and consultation in relation to occupational cancer were provided to Pennsylvania, Ohio, Colorado, Connecticut, New Jersey, New Hampshire, New York, and California State health departments; to the medical schools of the Universities of Pittsburgh, Utah, Southern California and Colorado, and to the Chicago Medical School; to other Federal agencies including the Bureau of Mines, Department of Agriculture, Naval Gun Factory, and the Environmental Health Center regarding cancer hazards involved in the production of shale oils and synthetic oils produced by hydrogenation of coals, nitro-naphthalene, pesticides, herbicides and nickel. Studies were undertaken with several industries of cancerigenic hazards related to pitch used in the manufacture of paper conduits and of drinking water adsorbates found in a particular area. Staff members published 18 papers and prepared 16 manuscripts on environmental cancer, which were presented at various meetings throughout the country. The branch's "Environmental Respiratory Cancer" exhibit was shown at 12 meetings.

Indoctrination in practices of epidemiological environmental cancer surveys was provided to a new team of four professional investigators who formed the nucleus of a new section created in May 1952, designated as the Cancerigenic Field Studies Section. The name of the original Cancerigenic Studies Section was changed to Cancerigenic Research Studies Section and its functions limited to laboratory research in environmental cancer. In October 1952 this Section was transferred to the Research Medicine Branch; the Cancerigenic Field Studies Section was redesignated the Field Studies Section with Dr. William Baum as head, and its activities enlarged to include all types of field studies of the Cancer Control Branch. In particular, this section was augmented by a team of professional personnel (2 physicians, a nurse, and engineer) to carry out field investigations in occupational and environmental cancer. This team is directing its attention especially to occupational factors related to lung cancer. They have reviewed the work accomplished by occupational cancer surveys supported by grants and have evaluated the results to uncover leads which may be pursued in further field studies and to determine the methodology best suited for such studies. Preliminary steps have been taken to initiate field studies on tobacco, nickel, asbestos, radium, radioactive water, minerals in non-uranium mines, and cigarette smoking, in cooperation with various organizations throughout the country. In these studies the collaboration of the Biometrics Section has been enlisted and liaison with the Occupational Health Division of the Public Health Service has been augmented.

Nursing

The branch's activities in the nursing field, under the direction of Miss Rosalie Peterson, are designed to improve nursing care to cancer patients and to increase the nurse's effectiveness in cancer control activities. The program includes services to State health agencies and universities, cooperation with nursing groups in the improvement of cancer teaching in nursing schools, and the development of new educational tools. In an effort to extend available knowledge of cancer to the nursing profession, an education program has been undertaken with schools of nursing, universities, and other educational institutions. Toward this end a teacher's manual, "Cancer Nursing in the Basic Professional Nursing Curriculum," was prepared by the staff and placed in use throughout the nation. It is anticipated that this material will have a significant effect on the teaching of cancer to nurses. Teaching materials of various types, including a series of slides on breast prosthesis, an annotated bibliography of cancer references, and a compilation of available visual aids have been prepared by the staff for use of nurse educators.

Three articles designed to advance nurse education in cancer were published by staff members in professional nursing journals. A series of cancer nursing institutes was conducted in Virginia, Idaho, and Wyoming. Consultation service was provided to the State health departments of Colorado, Idaho, Utah, Wyoming, Montana, Massachusetts, Tennessee, Georgia, Texas, California, Oregon, Washington, Arizona, Illinois, Wisconsin, and Minnesota, as well as to the Delafield Hospital, New York, New York; Pondville Hospital, Walpole, Massachusetts, M. D. Anderson Hospital, Houston, Texas; and the Ellis Fischel Hospital, Columbia, Missouri. Field trips relative to cancer teaching in the nursing school curriculum were made to Minnesota, California, Oregon, Washington, North Carolina, Massachusetts, New York, Missouri, Michigan, Illinois, Montana, Colorado, and Utah.

Support of pilot studies for improving cancer teaching in four schools of nursing has been undertaken with the staff working closely with the faculties in the respective schools. In order to determine something of the nature and extent of the nursing problems of cancer patients, the staff organized and conducted a study of the home-care cancer-nursing problem with 56 agencies in 27 States participating. The study was completed early in 1952, and the analysis of the data compiled is under way.

General

The Branch has continued its program for the production of educational films with the American Cancer Society. The major portion of production work was completed on a public lung cancer film and a professional oral cancer film. The film, Breast Self-Examination, continued to set a record for print sales throughout this period and has been widely utilized. In this connection, a project was undertaken in the State of Iowa to determine its effectiveness by a showing to all women over 25 years of age. During the reporting period the film was shown to the majority of women in the State and showings are continuing. Prior to this undertaking, a State-wide cancer morbidity survey was conducted in collaboration with the Biometrics Section to provide baseline data for comparison after the intensive showing of the film. The data are being analyzed and at a future date the survey will be repeated to check the results of the film showings.

Efforts of the Branch to determine the extent of the cancer problem were furthered through analysis by the Biometrics Section of the data from the ten morbidity surveys conducted under the direction of the Branch in previous years. A final overall analysis now under way should provide valuable data on the size of the cancer problem.

TECHNICAL SERVICES

Dr. Gilcin F. Meadors is the chief of Technical Services. During the past 18 months the Institute's technical services in epidemiology and biometrics have been strengthened by placing more emphasis on research in these fields. Recruitment of additional medical officers will be undertaken as soon as as authorized, and Dr. A. G. Gilliam, head of the Epidemiology Section plans to assign them to the development of field studies in leukemia, lung cancer, and cancer of the breast and cervix. With the termination of the Documentation

Program, Dr. Edwin Hoffman and Mrs. Veronica Bennett were transferred to the Epidemiology Section, and usable portions of the files and facilities used by the Documentation Program staff were made available to various units of the Cancer Institute.

Mr. William M. Haenszel was appointed as the new head of the Biometrics Section shortly before the end of this report period. New activities are in the formative stage. Increased load of statistical consultation is anticipated in connection with the developing program of clinical cancer research and with new studies in epidemiology and environmental cancer.

Through the printed word, motion pictures, slides, exhibits, and radio and television shows the Cancer Reports Section, under direction of Mr. James F. Kieley, has continued to disseminate cancer information to lay, professional and scientific groups. Special reports and analyses prepared by the Section have improved transmission of cancer information within the Institute and have proved of value in various administrative functions.

The work of publishing the Journal of the National Cancer Institute and the review and clearance of scientific papers by NCI authors for publication in outside journals have been ably handled by Dr. Ross C. MacCardle and his staff of assistants.

Biometrics

This section renders consultative service to and conducts studies in cooperation with other sections of the National Cancer Institute and outside agencies, in addition to having major responsibilities for projects in the field of biometrics. Activities during the past 18 months included:

1. Tabulation and analysis of the data collected in the survey of morbidity from cancer conducted in ten metropolitan areas. Reports for Denver, Pittsburgh, New Orleans, Chicago, Birmingham, Dallas, and Detroit were published and the one for Philadelphia sent to the printer. More detailed tabulations pooling the experience of all ten areas have been completed.

2. Field work has been completed on a State-wide survey of morbidity from cancer in Iowa conducted in cooperation with the Iowa State Department of Health. Editing and coding of the returns is almost finished. This is the first State-wide survey to be conducted and will make available for the first time morbidity data for a rural population.

3. Completion of a report comparing cancer morbidity in Washington, D. C., with a number of other metropolitan areas.

4. In cooperation with the Field Investigation Section of the Cancer Control Branch, the Biometrics Section planned a survey of morbidity from cancer of the cervix in Memphis and Shelby County, Tennessee. The field work and statistical analysis have been done. The study provides information for evaluating the vaginal smear technique in a screening program to detect cancer of the cervix.

5. Publication of a report evaluating the pilot cancer register established in four Maryland counties in cooperation with the State Department of Health of Maryland. This report illustrates the type of information that can

be made available when a cancer register is used as an integral part of a cancer control service program.

6. Advice and consultation to a number of State health departments on problems involving cancer registers and cancer statistical activities.

7. In cooperation with the Cancer Control Branch, a semiannual State cancer control activity report form was developed. The form has been approved by the Association of State and Territorial Health Officers and is being used to collect comparable cancer control activity data from each State.

8. In cooperation with the Pathology Section, an epidemiological study of cancer of the genital system among Jewish women was started in Israel. All cases of genital cancer are being reported to the Ministry of Health so that morbidity rates can be computed for comparison with corresponding data for other populations. In addition each cancer patient, together with two controls without cancer, are interviewed to obtain information concerning possible etiological factors. A similar study also was started in New York, N. Y., including both the Jewish and non-Jewish population. A preliminary analysis of the findings in Israel and New York is now under way.

9. Assistance was given to NCI personnel in the design and analysis of experiments. In the past year, consultation was given to experimenters working in the following fields:

(a) Studies of anti-leukemic agents with respect to efficacy and toxicity to host.

(b) Optimal therapy with antibiotics and other drugs, including problems of drug resistance and superimposed infections.

(c) Evaluation of diagnostic tests for cancer and other diseases (including studies in the State Universities of Kansas, Tennessee and Washington).

(d) Radiation effects and the efficacy of various treatments for radiation damage.

(e) Mechanisms of tumor genesis and development and the genetic effects on tumor-takes.

(f) Embryonic growth and differentiation.

(g) Epidemiological studies on cancer of the cervix.

Cancer Information

The Cancer Reports Section of the Institute disseminates information through special publications, films, reports, and exhibits, through the usual public information media such as the press, radio, and television, and by collaboration with other agencies engaged in work on cancer. This involves compiling reports on research accomplishments and other activities, writing lectures, papers and articles, the preparation of publications for printing and distribution; designing motion pictures and slides, and distributing the finished product, designing and showing exhibits, preparation and production of radio and television programs, editing and clearance of manuscripts, answering individual inquiries, and day-to-day service to the newspapers and magazines through issuance of press releases, answering inquiries, arranging interviews, and assisting in coverage of lectures and conference programs. The Section also prepares various types of special reports and analyses for internal administrative use.

Reports

Annual reports on the work of the Institute, quarterly reports on recognition received by NCI staff members, semiannual reports on papers published in outside journals and abstracts of these papers for use by NCI staff members were prepared.

Publications

New publications edited, cleared and otherwise processed by the Section for publication included: The Proceedings of the First Conference on Cancer Diagnostic Tests; Cancer Control: A Manual for Public Health Officers; Cancer Nursing in the Basic Professional Nursing Curriculum; A summary Progress Report of Cancer Control Activities for the 5-year Period 1947-51; Facing the Facts about Cancer; A bibliography of Cytologic Diagnosis; and eight reports in the Cancer Morbidity Series. Two leaflets, An Invitation From Your Doctor, and Vaginal Smear for the Early Detection of Uterine Cancer, were produced for the Memphis-Shelby County (Tenn.) Cancer Control Project.

A new brochure on the Institute was written. The Cancer Control Letter was prepared and issued monthly. Work was begun on a new edition of Cancer Services and Facilities in the United States.

Exhibits

Three new exhibits were designed and constructed: one on oral cancer, one on the research grants program, and one on Oral Cancer and the Dentist. The last, prepared for the annual meeting of the American Dental Association, won honorable mention. The exhibit, Environmental Respiratory Cancer, was renovated and displayed at the annual meeting of the American Association for the Advancement of Science. Photographs and an exhibit of NCI publications were supplied for the PHS exhibit at the American Public Health Association meeting.

Films

Uterine Cancer: The Problem of Early Diagnosis, the fourth film in the diagnostic series, was released with a special program at the AMA clinical session in Los Angeles in December 1951. Distribution was continued of this and the first three in the series, as well as Breast Self-Examination (1,414 prints sold) and Challenge: Science Against Cancer (both shown at the Montevideo film festival). Gastrointestinal Cancer: The Problem of Early Diagnosis was awarded a diploma of merit in the Venice Film Festival. Most of these films have been placed in United States embassies abroad by the Department of State.

Slides

A series of slides on oral cancer was prepared, and 100 sets of 40 slides each produced for distribution to dental schools and practicing dentists. One hundred sixty slides were prepared for speeches and lectures by NCI staff members. A series of 8 slides for nurses on breast prothesis was distributed. A series of slides for nurses on Self-Examination of the Female Breast was completed.

Inquiries

Approximately 2,800 inquiries were handled requiring 1,289 form replies, 783 original letters, 677 telephone calls, and distribution of over 15,000 pieces of literature.

Speeches, Articles

Thirty-nine articles were written for presentation or publication. Still pictures in connection with articles were supplied as requested. A picture file was maintained for current use.

Releases and Services to the Press

Releases to the press numbered 74. These included 29 general releases (morbidity survey series, grants, etc.), 7 to professional journals, 12 background statements on scientific papers scheduled for presentation, and 26 summaries of research accomplishments. Science writers and reporters representing national magazines, newspapers, and press wire services were furnished information on NCI activities and when necessary, interviews were arranged for them with staff members.

Radio and Television

Requests were filled for material for radio and television programs including appearances of the Surgeon General, the Director, NCI, and Institute staff members. Materials were prepared for use on the Johns Hopkins Science Review and the All Star News TV programs. Plans were initiated to produce a series of public educational TV film programs on cancer control. These will be made available to all TV stations.

Epidemiology

The program of the Epidemiology Section may be divided into five general objectives:

1. Analysis of comprehensive epidemiological records collected by former personnel of the NCI in a study instituted by Dr. Scheele. These records are being utilized (a) to evaluate the usefulness of case histories in the epidemiological study of human cancer; (b) to develop more adequate and precise methods of analyzing such records; and (c) to test and extend observations of the kind that have previously been made with such records.

2. Study of the geographic distribution of fatal cancer in the United States.

3. Provision of epidemiological consultation for others in the NCI and elsewhere.

4. Stimulation of epidemiological studies outside the Service.

5. Training of epidemiological personnel and initiating of field studies.

Accomplishments

1. Records of cases of cancer of the breast and of the cervix, together with other illnesses for comparison, have been analyzed with the view of determining the relationship of such factors as fertility, menarche, menopause, lactation, and marital status with these diseases. The study on fertility has been completed. The basic data for the other factors, except lactation, have been compiled. A more precise method of analysis has been devised for the fertility study and is being modified for the others.

The study of the association between smoking and various types of cancer has been completed, but is being extended to include another site. The associations developed are in general agreement with those previously published but internal evidence suggests caution in interpreting the associations as being etiological.

Investigation of a method for analyzing occupational histories continues.

2. Study of the distribution of leukemia by counties, which was planned as a trial run for contemplated studies on all important cancer sites, has been slowed initially by lack of personnel. Basic data are now being compiled for cancer of the lung. As a by-product, a study has been made of the age, race and sex selection of leukemia and the lymphomas. Personnel are now available and as the 1950 Census data are completed these studies will run concurrently.

3. Considerable consultation has been provided the Cancerigenic Field Studies Section in the planning and conduct of their epidemiological studies.

Consultation has been provided the Division of Environmental Health of the Bureau of State Services regarding studies of hazards in uranium mining and processing.

4. Attempts have been made to stimulate State Health Departments and Schools of Public Health to undertake epidemiological studies. To this end seminars on cancer epidemiology have been conducted at the Michigan, Pittsburgh, and Columbia Schools of Public Health. Assistance has been given the Department of Epidemiology at Michigan in initiating a field study of leukemia, and the Arizona State Health Department in planning a study of cancer among the Navajos. This Section will provide guidance in the latter study and analysis of results if the State is able to get funds for certain aspects of the field work.

5. Funds have recently become available to secure two Senior Assistant Surgeons for long-term training and working assignments. Field studies in leukemia, lung cancer, and cancer of the breast and cervix are tentatively

earmarked for these men as they become available. Training assignment will include a detail to a school of public health for academic work in epidemiology and clinical cancer while actively engaged in a field study. Dr. Meadors is spending part of his time on preliminary planning and exploratory field work for the study of leukemia.

Scientific Papers

The editorial office has reviewed 72 scientific papers by NCI staff and 54 by outside authors who wished to publish in the Journal of the National Cancer Institute; 275 scientific papers by NCI staff members were cleared for publication in outside journals. In this activity the office has had the assistance of five associate editors, an eight-member editorial committee, and an advisory editorial board made up of representative scientists from the United States and several foreign countries.

The Journal of the National Cancer Institute is one of three devoted exclusively to cancer published in the United States. It is issued bimonthly, has an average of 240 pages per issue, and a circulation of over 1400 copies, including 535 paid subscriptions.

NATIONAL HEART INSTITUTE

James Watt, Director

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NATIONAL HEART INSTITUTE

July 1, 1951--December 31, 1952

Introduction

Heart disease is responsible for over half of the Nation's deaths. It also accounts for a large portion of the disabled. Because of heart disease, millions of Americans are hindered to some degree from living full, normal, active lives.

The National Heart Institute spearheads the total heart program of the Public Health Service; this was specifically authorized in 1948 by Congressional enactment of the National Heart Act. The program has two main goals: (1) to find new and better ways of preventing, diagnosing, treating and curing heart disease and (2) to see that existing knowledge is fully applied to reduce death, disability, and suffering caused by heart disease.

Laboratory and clinical research conducted by the Institute progressed significantly throughout the year, developing much new knowledge important to the understanding and the management of heart and blood vessel diseases. The program of research grants, by which investigations in institutions throughout the country were fostered and supported, also resulted in many valuable discoveries. Training activities, including teaching grants to medical schools and other institutions, research fellowships, and clinical traineeships, helped to relieve shortages of medical and scientific personnel skilled in the cardiovascular field. Aid to the States and Territories was provided in conjunction with the Bureau of State Services and contributed materially to the solid growth of community programs and the practical application of the fruits of research.

Research Achievements

Progress was made in research relating to arteriosclerosis and coronary artery disease. Utilizing a combined chemical and physical methodology, some of the factors which determine the physical state of fatty materials in plasma have been discovered. There exists in the body a system consisting of at least four component parts, a deficiency of any part of which would result in a marked disturbance of fat transport and presumably would foster conditions essential for the development of atherosclerosis. A protein in plasma has been isolated and partly purified which combines with heparin, an anticoagulant, in the presence of another specific protein contained in either stomach or lung to form a complex which has the ability to change the physical state of fat-containing molecules in the plasma. It does this only in the presence of a third protein isolable and partially purified which is also contained within normal plasma. This complex is called a "clearing factor" since it has the ability to clear the milky condition of the blood which follows a fat meal. Of greater significance, however, is its ability to change that portion of the fat which physically combines with protein in such a way as to foster the deposition of fat in the arterial wall. The breaking down of this complex system into component parts is a major step in the development of our knowledge of atherosclerosis.

Cardiac failure is a serious and continuing problem in heart disease. This is so because no specific therapy exists and there is little basic understanding of the biochemical and biophysical mechanisms which underlie the normal or abnormal functioning of the contracting heart muscle. In the Institute's investigations, a frontal attack has been made on the problem through use of experimental preparations. Failure of the heart or symptoms of cardiac deficiency were produced by interfering with the heart directly (adhesive pericarditis), by producing a chronic overburden on the heart to force a greatly increased output per minute (through arterio-venous fistulae), and by preventing the free return of blood to the venous side of the heart (partial closing of certain great veins). Surgical removal of certain components of the endocrine system has permitted study of the role of these organs in the development and maintenance of the abnormal condition encountered in cardiac failure. Observations including all of these preparations have confirmed the importance of the kidney and the endocrine glands controlling it in the development of circulatory failure. It was also found that the liver plays a role, as yet unknown and unexplained, in controlling the smaller elements of the vascular system which must remain partially contracted if blood pressure is to be at a normal level. In addition, the role of diet, both from the standpoint of salt and protein intake, has been more clearly defined. It is now certain that some renal changes commonly believed to be of primary importance in the development of disturbances in the ability to excrete salt and water are, in fact, secondary to a loss of effective protein from the circulation.

One investigation conducted in 1952 represents a rather unique approach to a most fundamental problem in the field of cardiovascular function. For many years physicians have believed that certain chemical substances extractible from the heart itself have the ability to improve the effectiveness of cardiac activity when this is impaired because of disease. Systematic study of one such substance during the year showed it to be without specific useful effect. However, chemical compounds related to digitalis have been described as present in animal tissue. These so-called Bufo toxins, secreted by a gland under the skin of certain South American toads, have a striking effect on cardiac tissue and are similar in many respects to the digitalis preparations derivable from plant sources. In the belief that these are normally occurring substances and have a function in the normal heart of the same general nature as digitalis, an attempt was made to develop methods for their isolation and estimation in trace amounts. These techniques are now available and will make possible an intelligent approach to the problem of cardiac hormones.

In the field of hypertension, considerable progress was made in the study of certain chemical agents normally present in the blood which have an ability to influence blood pressure. One of these, adrenalin, was studied from the standpoint of its biosynthesis in the adrenal gland. Radioactive material was used in order to reveal the normal pathway of formation of this agent, to determine its rate of formation and its maximal rate of release. It is evident from these studies that the release of adrenalin in the resting state is too low for it to have an important effect on blood pressure. However, it was also demonstrated that its rate of release in the normal gland is sufficiently high under conditions of stress to contribute to an elevation of blood pressure.

In the same general field it has been possible to synthesize a compound, serotonin, normally present in the blood and liberated into plasma during the clotting process. This compound appears to be important in stopping hemorrhage and may also be important in the general control and support of the circulation. The latter possibility exists because the compound is widely distributed in organs containing smooth muscle and because closely related chemical compounds, heretofore not known, have been found in the adrenal medulla.

Investigations of the Institute aimed at improving the use of therapeutic agents already available and developing new therapeutic agents continued with notable success. The intravenous anesthetic agent has now advanced to the stage of fairly wide-scale clinical investigation in order to determine its proper place in relation to other anesthetics. Studies of anti-clotting agents continue, but the major advances in this particular area were achieved in 1951, and work during 1952 has mainly been concerned with verifying the 1951 findings. Procaine amide continues to show wide usefulness in its ability to abolish the fatal irregular heart rhythms which frequently follow coronary thrombosis and occur during anesthesia with a number of commonly used anesthetics. Its use now extends to preventing this irregular heart rhythm by prior administration in both of these situations. The drug is available at low cost and is being manufactured by at least three of the major pharmaceutical houses.

Studies in the field of gerontology emphasize the cardiovascular system, the kidney, metabolism, endocrinology, and psychology. The emphasis of the program has been to determine biochemical, physiological and psychological constants which describe the over-all process of aging. It is not until such information is available that a truly experimental approach to the problem is possible. It can be reported that there is a progressive deterioration in many physiological systems with age which is amenable to a fair degree of measurement. It is of some significance that the changes noted to date are due not so much to a change in cellular activity of the effector organ, i.e., the muscle, kidney, etc., but rather due to a loss of organ substance or some interference with the central control of the organ.

Advances Through Research Grants

More than 600 grants recommended by the National Advisory Heart Council and approved by the Surgeon General of the Public Health Service supported investigations in over 100 universities and hospitals during the period July 1, 1951 through December 31, 1952. The total amount spent in support of research was approximately $7,200,000. These research projects covered a vast range of subjects and cast important new light on a number of cardiovascular disease problems. The following are a few of the many significant achievements resulting from the research grants program.

First results of cooperative clinical studies investigating the merits of ACTH, cortisone, and aspirin in the treatment of rheumatic fever showed that each is effective and that the acute symptoms usually subside with use of any of the three agents. Certain individual symptoms appear to be more favorably affected by one or another of the drugs, but no consistent pattern warrants a conclusion as yet as to which drug is most effective for control of the acute illness. Comparative effectiveness of the three drugs in preventing the heart disease which often follows attacks of rheumatic fever is being investigated.

An important advance in the development of effective blood pressure reducing agents was disclosed by studies of the drug hexamethonium. The drug offers great promise of reducing arterial pressure in patients with many forms of hypertension, including critical malignant types, and appears to produce a more complete blockade of sympathetic nerve impulses than any other agent so far studied in man. Two other drugs have been found which provide relief for certain types of high blood pressure - 1-hydrazino-phthalazine and 1-hydrazino-4-methyl-phthalazine. Following successful tests on hypertensive dogs, clinical application on patients revealed considerable sustained action in lowering blood pressure in hypertension of nervous origin, but little effect was seen in hypertension associated with the kidney.

Research efforts in the field of lipid-bearing molecules produced new data which promises to result in eventual benefit for persons with arteriosclerosis. Continuing work on separation of large abnormal molecules from blood serum has revealed a new range of molecules which, when present in combination with the Sf 10-20 types, appear to be more closely associated with atherosclerosis than either alone. It has been found that the two major classes of lipoproteins, the Sf 10-20 class and the Sf 20-100 class, contain essentially all of the serum lipids involved in atherosclerosis. These classes make up only 10 to 15 percent of the total serum cholesterol. Another study has shown that a significant relationship exists between obesity and some classes of lipoproteins. While the Sf 10-20 range of molecules is not affected by food intake, the Sf 35-100 molecules show considerable increases in level after the eating of fats. These findings may offer an adequate explanation of the high frequency of atherosclerosis accompanying the obesity state. Since weight loss appears to reduce the Sf 35-100 levels in many persons, control of obesity may be important in lessening the hazards of atherosclerosis.

A brilliant achievement was the development of a plastic artificial valve for the surgical treatment of an impaired aortic valve. In cases where the aortic valve is defective and allows blood to back up, the heart is frequently seriously over-worked and congestive failure may develop. In the new method, after removing a section of the aorta, the plastic valve is inserted in the blood vessel. The valve, about two inches long, contains a small plastic ball which moves to one end to allow blood to flow through and is pulled to the other end when the heart relaxes, thus preventing the blood from flowing back. The device has been successfully installed in a human patient.

Medical history was made with the use of a mechanical heart which efficiently carried the circulation while the patient's own heart was being operated on. Several types of heart machines are being developed and with their continued improvement it is anticipated that a dependable and satisfactory instrument for clinical use will be available in the foreseeable future. The general availability of such an instrument will make possible much heart surgery which cannot now be undertaken.

Epidemiological Highlights

The first phase of the heart disease epidemiology study being carried on in Framingham, Massachusetts, was completed in 1952 with the completion of initial examinations of the cross-section population group. This research, conducted by the National Heart Institute in cooperation with State and local health departments and medical societies, is attempting to obtain information on the factors involved in the development and progression of hypertensive and arteriosclerotic heart disease in adult life. Repeat examinations will be given every two years over an extended period to those persons participating in the study. With completion of the first phase, data is now being tabulated which will give for the first time an accurate indication of the prevalence of heart disease in a typical community. It is believed that the proportions found in Framingham will be generally true for many parts of the Nation.

Another important development in 1952 was the formulation of plans for a nation-wide campaign for prevention of rheumatic fever, the cause of rheumatic heart disease. The campaign will be launched in January 1953 with simultaneous publication in several journals of a statement of treatment recommendations issued by the Council on Rheumatic Fever and Congenital Heart Disease of the American Heart Association. Cumulative clinical experience has established that most initial and recurrent attacks of rheumatic fever can be prevented by early and adequate penicillin treatment of the precipitating streptococcal infection. The National Heart Institute is cooperating with the Division of Chronic Disease and Tuberculosis, Bureau of State Services, and with the American Heart Association, in furthering the preventive campaign.

Publication in April 1952 of the booklet "Diseases of the Heart and Blood Vessels--Facts and Figures," by the American Heart Association in cooperation with the National Heart Institute, filled the need for an authentic, understandable summary of facts about the cardiovascular diseases. The booklet has been particularly useful since it represents a uniform statement in the difficult field of heart disease statistics by the government and the chief voluntary agency concerned.

Physician education in the most recent developments in the cardiovascular diseases has been furthered by a new bi-monthly periodical, "The Heart Bulletin" for the general practitioner of medicine. This publication, which is distributed by the Medical Arts Publishing Foundation of Houston, Texas, was developed with the consultation of the National Heart Institute and the National Advisory Heart Council and in cooperation with the American Heart Association. The circulation of "The Heart Bulletin," the first issue of which appeared in March 1952, had reached more than 60,000 by the end of the year.

Preliminary planning was begun during the year for the Second International Congress of Cardiology to be held in 1954 at Washington, D. C., under the cosponsorship of the National Heart Institute and the American Heart Association.

RESEARCH BRANCH

The research program of the National Heart Institute is directed toward increasing fundamental and clinical knowledge of the underlying disease processes affecting the heart and circulatory system, and toward evolving information which will permit the prevention or amelioration of these diseases. Research activities are concerned with the total cardiovascular system, the kidney, and the endocrinological and nervous factors which control these organ systems; disease states, and their etiological agents, which are important factors in the development of cardiovascular and renal disease; and gerontology.

During 1952, laboratory and combined laboratory and clinical studies developed considerable new knowledge important to the understanding and management of the cardiovascular diseases. Some of the highlights of this progress are given in Part I of this report. Detailed reports of the work of the laboratories and clinics follow.

Laboratory of Chemical Pharmacology

Bernard B. Brodie, Chief, directs the work in this laboratory, primarily concerned with basic biochemical pharmacology. It covers a range of investigations on the mechanism of action of therapeutic agents, on the biosynthesis of hormonal agents, on the biochemical mechanisms which metabolize drugs, on the discrete cellular bindings of drugs with various tissues, and on the physiological disposition and chemical fate of drugs in man. Clues stemming from these studies are extrapolated to the development of new or more suitable cardiovascular agents.

Physiological Disposition and Chemical Fate of Drugs in the Body. Investigators: Julius Axelrod, Elwood Titus, Sidney Udenfriend, John Burns, Bert La Du, Chozo Mitoma, Jack Cooper, Gertrude Quinn, Lewis Aronow, Jules Reichenthal, and Bernard B. Brodie.

This work concerns the fate of therapeutic agents in the body, stressing the clinical and chemotherapeutic implications of these studies; how these studies can lead to a more rational use of drugs; define the limitations of a particular class of drugs; and, finally, suggest the synthesis of better drugs.

The medical profession learns, by clinical experience, to derive the maximum therapeutic effect from a drug. With certain drugs this has taken decades of experience. It is now possible to circumvent the old method of clinical trial and error. The availability of short cuts is of prime importance in the development of new drugs and may prevent a useful agent from being prematurely discarded. The modern approach is based on the premise that the effect of a drug is related to its plasma level. This approach requires a fundamental knowledge of the fate of a drug in the body in order to elucidate these factors which affect the drug plasma level. The factors which influence the plasma level and therefore the effectiveness of a drug are absorption from the gut, urinary excretion, tissue localization, and rate of metabolic transformation. Such studies have already led to a more rational use of a number of drugs including anticoagulants, intravenous anesthetics, and antimalarials. It has resulted in the development of new drugs, e.g., procaine amide for heart arrhythmias; Rapidal, a new anesthetic; and N-acetyl-p-aminophenol, a new analgesic.

Methods for Estimation of Drugs and Isolation of Drug Metabolites. Simple micro methods are needed for the determination of drugs in biological tissues. A systematic approach for the estimation of drugs has been previously described. These methods have been modified so that many drugs may be determined in a drop of plasma. In the past 1½ years methods were developed for the estimation of N-alkyl barbiturates, various narcotic analgesics, Dicoumarin type anticoagulants, anti-inflammatory agents, sympathomimetic amines, and adrenergic blocking agents.

An isotope labelling technic was developed whereby it is possible to administer a drug and to isolate from urine water-soluble transformation products even though their structures are unpredictable. This technic was successfully applied to a study of the fate of Nembutal and is now being used to study a newly discovered pathway of tryptophan metabolism.

Urinary Excretion. Our work indicates that the kidney plays a relatively minor role in drug excretion, as most drugs are almost entirely metabolized. However, Priscoline, a drug used in peripheral vascular disease, is excreted unchanged. It is significant in thinking in terms of drug mechanisms that a compound can be chemically inert in vivo yet exhibit marked pharmacological activity. The manner in which Priscoline is handled by the kidney was studied in collaboration with Drs. R. W. Berliner and J. Orloff (Laboratory of Kidney and Electrolyte Metabolism), and it was found to be secreted by kidney tubules at the same rate as p-amino-hippuric acid but by a different mechanism. Further studies of the manner in which the kidney excretes basic organic compounds will be carried on.

Localization in Tissues. It is becoming evident that few drugs would exert a significant effect were it not for the storage depots of the body. Most drugs with a long duration of action are characterized by extensive and reversible localization in some tissue depot. This protects drugs by withdrawing them from body fluids and thus slowing their rates of biotransformation and urinary excretion.

Drugs are localized in a number of ways. One way is by deposition in body fat. We found that the Dibenamine type drugs, agents of potential use in hypertension, have a long duration of action due to their extensive localization in fat from which they are only slowly released. Acetylmethadol, an analgesic agent which produces an effect of considerable duration, owes this property to its extensive fat localization. This drug is said to be too toxic for human use, but it has provided a clue toward the development of a long lasting analgesic. The intravenous barbiturates such as Pentothal and Evipal metabolize slowly and are short acting not because they are rapidly metabolized, as thought, but because they have a high affinity for fat. They rapidly diffuse from brain and other tissues into body fat. This explains their usefulness in operative procedures of short duration, but their limited applicability in operative procedures of long duration. These findings have led to a more rational use of Pentothal as well as directing attention toward the need for a more unstable intravenous anesthetic.

Further work is designed to define other depots, probably protein in nature, which localize drugs. In particular, Dr. G. M. Tomkins is studying reversible combination between nucleoproteins and certain organic bases such as the antimalarial drug atabrine, which accounts for the extensive tissue localization of these compounds.

Metabolic Transformation. The duration of action of a drug is limited by its stability in the body. Little is known about the relationship between the structure of drugs and their stability in the body or about the biochemical mechanisms which inactivate them. However, it is becoming more and more apparent that drug biotransformations can be described in terms of a relatively few biochemical mechanisms. We have studied two of these in some detail.

(1) Dealkylation. Many drugs are alkylamines. We have found that the body almost invariably detaches the alkyl groups from the nitrogen atom; for instance, with ephedrine, aminopyrine, methylamphetamine, Regitine, and Demerol. The biochemical system responsible is in liver and has been partially purified. Preliminary results suggest that a common enzyme is involved whether the dealkylation involves a methyl, ethyl, or butyl group.

SKF, a relatively nontoxic substance with little or no pharmacological action, was found to inhibit the dealkylation system both in vitro and in the intact animal. It also inhibits the metabolism of various barbiturates which are inactivated by oxidation of the side chain. This suggests that dealkylation is also an oxidative mechanism. Pharmacologically, the action of SKF is reflected in a dramatic prolongation of the pharmacological effects of various narcotic analgesics (alkylamines) and barbiturates when animals are pretreated with the compound. It is planned to purify the dealkylation and side-chain oxidation systems and to use SKF as a tool in unraveling their common characteristics and their normal role in the body economy.

(2) Oxidation of Aromatic Compounds. A large number of aromatic drugs, e.g., acetanilide, aniline, theophylline, salicylic acid, and amphetamine, are oxidized in the body to the corresponding phenols. We have found that a model system consisting of ascorbic acid and Fe^{++} also oxidizes these drugs to yield the identical products formed in the body. Presumably the model system operates by introducing positively charged hydroxyl (OH^+) groups into the aromatic ring. It is probable that a similar type of reaction occurs in vivo, i.e., what has been termed oxidation is in reality the substitution of a hydroxyl group for a hydrogen on the benzene ring. We have shown that ascorbic acid also plays a role in this reaction in vivo, since guinea pigs depleted of ascorbic acid have an impaired ability to oxidize drugs. Ascorbic acid also plays some role in the metabolism of other types of drugs, since rats given chloretone and barbiturates tremendously increase their synthesis and excretion of the vitamin. Nothing is known about the chemical role of ascorbic acid in vivo, and this work provides a wedge in this direction.

Although drugs are hydroxylated by a nonspecific biochemical mechanism, there appears to exist more specific mechanisms for the hydroxylation of normally occurring substrates. For instance, phenylanine and tryptophan are oxidized to phenols by quite specific hydroxylation mechanisms. These new types of enzymes are being exhaustively studied to find out how the body introduces hydroxyl groups.

Our work has turned up a marked species variation in the biotransformation of drugs which is both qualitative and quantitative. Ordinarily, potential therapeutic agents are first screened for activity and toxicity in animals. Species variation makes it difficult to carry over results into man. A comparative study of biochemical mechanisms which inactivate drugs has been undertaken. The results of this study should aid in the choice of suitable animals for screening the activity and toxicity of various classes of drugs. Parallel studies will evaluate the influence of age and sex on drug metabolism.

Development of New Compounds for Pharmacological and Clinical Studies. Investigators: John Burns, Murray Weiner, Arthur Schulert, Bert La Due and Bernard B. Brodie.

Anticoagulants. In an attempt to develop a synthetic substitute for Heparin, a number of sulfuric acid and sulfonic acid esters, mainly dyes, were tested in vitro for their effect on the clotting mechanism. Active compounds were found but none of them had appreciable activity in the intact animal. We are still looking for a Dicumarol type drug, less capricious in its biological behavior. Dr. H. B. Wood and Dr. E. C. Horning (Laboratory of Chemistry of Natural Products) have synthesized some anticoagulants of the Dicumarol type. An active compound is being studied.

Barbiturates. Pentothal is too stable in the body to be short-acting after sustained administration. In collaboration with E. R. Squibb, we have developed Rapidal, an intravenous anesthetic. For comparable depth of anesthesia, subjects awake sooner and with considerably less postanesthetic somnolence than after Pentothal. This product is now being given extensive clinical trial.

In collaboration with Eli Lilly, the potentialities of the N-alkyl thiobarbiturates are being investigated. Preliminary studies with these compounds show that the recovery time after large doses is considerably shorter and postoperative somnolence much less than following Pentothal.

Drug potentiating agents. In collaboration with Smith, Kline, and French, and Dr. Wood and Dr. Horning, derivatives of SKF are being screened. This type of compound while almost devoid of pharmacological activity, markedly prolongs the action of analgesics and anticonvulsants by blocking their metabolic transformation. These derivatives will also be tested against malaria, since SKF shows some antimalarial activity.

Tyrosine Oxidation. Investigator: Bert La Du.

Further studies on the intermediary metabolism of tyrosine have outlined the intermediates in its breakdown to fumaric and acetoacetic acids. Partial purification of the enzyme system involved in one of the steps, the oxidation of p-hydroxphenylpyruvic acid, has been obtained. This reaction appears to require ascorbic acid. This may be important since a definite chemical role for ascorbic acid has not been tied down. Further purification of this enzyme system is in progress.

Biological Significance of Choline. Investigators: Bert La Due and Bernard B. Brodie.

Difficulties met in the method for estimating free choline in plasma have finally been resolved. The procedure is being applied to studies of the metabolism and synthesis of choline in vivo. There appears to be a mechanism for maintaining constant the plasma choline level. Even after large intravenous or oral doses of choline to animals the plasma choline concentration rapidly returns to the pretreatment level. After the injection of choline labelled with C^{14} in the ethanol moiety, only a trace of radioactivity appears in urine and only a fraction in the respired air in 24 hours. This indicates that the choline is probably transformed to relatively stable compounds. The nature of these products is being investigated.

Biogenesis of Hormones. Investigators: Elwood Titus, Sidney Udenfriend, Carroll Clark, and Jack Cooper.

A prerequisite to an over-all study of cardiovascular disease is knowledge of the mechanisms by which the body elaborates the hormones which mediate the activities of the cardiovascular system. It is obvious that physiological factors or chemical agents affecting the formation of these substances will markedly alter physiological function. The purpose of this program is to determine which precursors the body uses in the synthesis of three such agents, adrenaline, noradrenaline, and serotonin, and to study the enzymes involved in the synthetic reactions.

We have found that adrenaline and noradrenaline is formed from phenylalanine, which via tyrosine, goes through a series of chemical changes to yield the adrenalines. Normally, the turn-over of adrenaline in the adrenal gland is extraordinarily slow. One of the intermediate enzymes, dihydroxyphenylalanine decarboxylase, has been considerably purified. Work is continuing to establish the other compounds and enzymes in the chain of synthetic reactions leading to adrenaline.

The formation of serotonin from tryptophan has been demonstrated to occur by way of a new metabolic pathway involving the formation of a hitherto unknown amino acid, 5-hydroxytryptophan. An enzyme catalyzing the decarboxylation of the latter compound to serotonin has been isolated from kidney in partially purified form. Other enzymes involved in the synthesis will be studied, and the fate of serotonin in the body will be followed.

Studies with Butazolidin, a Non-Steroid Anti-Inflammatory Agent. Investigators: John Burns, Murray Weiner, Theodore Chenkin and Bernard B. Brodie. In collaboration with Dr. E. Lowman, Institute for Rehabilitation, and Dr. J. M. Steele, Goldwater Memorial Hospital.

The implications of a simple, nonsteroidal compound for the treatment of rheumatoid arthritis, gout and other inflammatory diseases are profound and for this reason Butazolidin has merited a detailed study. In patients with severe rheumatoid arthritis with evidence of joint inflammation, etc., we found the drug exerted definite anti-inflammatory effects and increase in joint motion comparable to cortisone. In patients in whom the drug had no effect (i.e., analgesia only) cortisone also usually elicited no effect. Butazolidin, as does cortisone, causes a marked retention of sodium, chloride, and water. It also causes some retention of potassium, whereas cortisone and ACTH cause an excretion of this ion. Unlike cortisone and ACTH, Butazolidin does not affect the concentration of sodium and potassium in saliva. These results suggest a different mechanism in its effect on electrolyte excretion. Unlike ACTH, Butazolidin does not increase excretion of ketosteroids, depress circulatory eosinophils, or affect carbohydrate metabolism. This suggests that Butazolidin does not exert its effects through the pituitary-adrenal axis. Butazolidin has a number of side-effects causing discontinuance of therapy in 25 percent of patients. Certain of these are similar to those produced by cortisone, such as edema, congestive heart failure, and reactivation of peptic ulcers. Other side effects are nausea, vomiting, and dermatitis. Unlike cortisone or ACTH, it does not produce hormonal effects.

The chemical fate of the drug has been studied and several metabolites isolated. These will be tested to assay the part they play in the activity and toxicity of the drug.

Butazolidin is probably a landmark in medicine since it is the first nonsteroidal compound to have definite cortisone-like activity in a number of inflammatory diseases. It is not the final answer, however, as a compound with less side effects is needed. We have instituted a collaborative effort with Geigy Pharmaceuticals, the National Institute of Arthritis and Metabolic Diseases (Dr. J. J. Bunim), and Goldwater Memorial Hospital (Dr. J. M. Steele) to develop a better anti-inflammatory agent.

Laboratory of Chemistry of Natural Products

Evan C. Horning is chief of this laboratory. Research projects include studies on the isolation and identification of materials of biochemical interest from natural sources, and fundamental studies on the structure and reactions of organic compounds related to life processes. Joint projects with the Laboratory of Chemical Pharmacology involve the study of drug action and drug metabolism through the synthesis of active agents or metabolic products.

Investigations of Physiologically Active Material from Plant Sources. Study of plant materials affecting the cardiovascular system is in progress. This work is concerned with a search for physiologically active agents, which are usually alkaloids or glycosides, but which may also fall into other chemical classifications, and it involves the isolation of active agents and the determination of their structure. Pharmacological and, in some cases, clinical, studies are correlated with the chemical studies. The work is being carried on with the cooperation of the Bureau of Plant Industry of the U. S. Department of Agriculture and with the pharmacological and clinical laboratories of the National Heart Institute. The materials selected for study are those for which physiological activity has been reported, or which are botanically related to plant materials of reported activity.

Reports of the influence of plant materials on the cardiovascular system are frequently incomplete and conflicting. It is particularly difficult to evaluate reports of hypotensive activity, yet this is one of the most important areas of work in this field. Crataegus oxyacantha has been used in the United States and In Europe in extract form as a hypotensive agent, but a clinical investigation under Dr. Luther Terry (Clinic of General Medicine and Experimental Therapeutics) showed no evidence of activity and chemical studies were therefore not undertaken. Currently, several other materials which are reported to depress blood pressure or to have adrenolytic activity are under investigation. A new crystalline alkaloid has been isolated from Vinca minor, a common trailing evergreen vine, as a consequence of old reports that Vinca species contain alkaloids which depress blood pressure. A method of isolation has been developed for the alkaloid, and its structure is studied by Dr. S. M. Goodwin. It has been known for many years that plants of the Ericaceae family, including the mountain laurel and native rhododendron species, contain a potent active principle which affects the cardiovascular system. Previous reports on the structure and pharmacological activity of the active agent are incomplete, and the agent was known only as an impure material. From sample of Phododendron maximum obtained in Virginia, Dr. H. B. Wood isolated for the first time a pure crystalline glycoside which is active in very small amounts. Its chemical structure is under investigation, and larger samples are being prepared for detailed pharmacological evaluation. Plants of the Amaryllis family are widely distributed over the world, but only two sub-groups, one native to Japan and the other native to Africa, contain appreciable amounts of alkaloids. The alkaloids of the Japanese species show a relatively low order of physiological activity, but those from the African species are much more potent. Boophane distichia, the "gif bol" of South Africa, was once used in the preparation of arrow poisons, and it is a member of the Amaryllis family. It has been found by Dr. V. L. Stromberg that there is a major new component in the alkaloid fraction of the African species which is not present in the Japanese species, and work is in process on the isolation of this component. Studies on the structure of the alkaloids gelsemine, aspidosperimine, and pereirine were carried out by Dr. Patrick. Other alkaloid fractions which have been isolated, but about which very little is known at present, include those from Cephalotaxus sp. and from Cassis marginata. In all of these cases the pharmacological examination is not complete. The Cephalotaxus problem is under investigation by Dr. H. Lloyd.

In general, these problems require the testing, by chemical or pharmacological methods, of plant materials or plant extracts. The next step is the isolation of a sufficient quantity of the active agent or agents for chemical study and for more detailed pharmacological study. Intensive chemical work is then usually required to determine the structure of the active compound. At the present time the preliminary chemical examinations are being carried out under the direction of Dr. V. L. Stromberg, and the isolation work for the group is under the direction of Dr. M. S. Fish.

These investigations will be continued and additional problems will be brought under intensive study. The materials which will be examined include Ornithogalum thyrsoides (South Africa), Picrasma crenata (Brazil), Urginea altissima (South Africa) and several genera in the Ameryllidaceae, Apocyanaceae, and Liliaceae families.

Studies on the Structure and Properties of Molecular Complexes. Molecular complexes have for many years been one of the least well understood groups of organic chemical materials. These substances in some cases are relatively labile combinations existing in the solid state, but which are dissociated in solution; in other cases the complex structure exists in the liquid phase but not in the solid phase, and in some cases the stability of a complex may approach that of a compound, and may show no evidence of dissociation in the solid state or in solution. The importance of these substances lies in the fact that they often may be intermediates in irreversible chemical reactions, with a consequent lowering of the activation energy.

The most recent and notable development in this field was the announcement last year of a new quantum-mechanical theory of structure for charge-transfer complexes by Dr. R. S. Mulliken of the University of Chicago. At the same time in this Laboratory an investigation of one class of charge-transfer complexes, those related to quinhydrone, was under way. This class was chosen for study because of its relationship to energy-transfer systems in biological reactions in which one-electron oxidation reduction is known to occur. This work was carried out by Dr. Stromberg, with contributions by Dr. H. Lloyd, Dr. M. S. Fish, and Dr. G. N. Walker. Several new conclusions about the structure of a number of organic compounds emerged from this work, but perhaps the most significant result from a biochemical point of view is the conclusion that the intermediate semiquinone in one-electron oxidation-reduction is a molecular complex.

Studies of Drug Metabolism. The project on intravenous anesthetics under Dr. Brodie indicated that Pentothal is converted into carboxylic acid on oxidation in humans. The proposed structure for the metabolite was confirmed by its synthesis by Dr. H. B. Wood. Further contributions to the study of barbiturates were made by Dr. Lloyd and Dr. Stromberg. The project on the metabolism of anticoagulants of the Tromexan and Dicoumarol type was aided by Dr. Wood, and a new active anticoagulant was prepared for study.

Investigations of the Structure and Reactions of Organic Compounds. These studies were primarily concerned with aspects of fundamental organic chemistry, where the compounds and the reactions were of interest because of biological implications. Investigations were carried out of the reactions of polyphosphoric acid, a linear plymeric anhydride related in structure to the polyphosphate chain frequently found in biological systems. A new method for accomplishing the Beckmann rearrangement, together with new information about these reactions, resulted from the work of Dr. Stromberg and Dr. Lloyd. Dr. Kissman developed a new indole synthesis, and Dr. G. N. Walker studied the cyclization of benzylsuccinic acids. The synthesis and rearrangement of quinols was studied by Dr. Goodwin in order to substantiate the mechanism of the rearrangement which occurs during the metabolic transformation of tyroside to homogentisic acid. An extensive investigation of ozonides and peroxy compounds was carried out by Dr. Witkop, Dr. Goodwin, Dr. Kissman, and Dr. Patrick. The compounds investigated were oxidation products of anils, phenylhydrozones, alloxan, various indoles, and derivatives of maleic and fumaric acids.

Synthesis of Compounds of Biological Interest. A cooperative program between Dr. B. Witkop and A. Ek resulted in the synthesis of a number of 5- and 7-hydroxytryptamines, including serotonin (5-hydrocytryptamine).

A synthesis of compounds related to podophyllotoxin was undertaken by Dr. G. N. Walker, and the desired products containing the entire carbon-oxygen skeleton of podophyllotoxin were obtained.

Laboratories of Cellular Physiology and Metabolism (Combined Report)

Activities of these two laboratories (Christian B. Anfinsen, Chief) are considered in this report as a single, loosely integrated unit, as the small size of the Metabolism group relative to that of the Laboratory of Cellular Physiology and of other laboratories in the Heart Institute neither requires nor justifies separate summary. The increasing research effort as well as the considerably augmented staff and Clinical Center housing plans of the Laboratory of Metabolism will, however, in the coming few months, lead to administrative and spatial separation of the combined groups.

The research activities of the Laboratory of Metabolism are primarily concerned with basic biochemical and physiological studies on metabolic diseases and diseases involving metabolic disorders (e.g., atherosclerosis, diabetes, nephrosis, thyroid disease, etc.). Direct clinical application is, of course, impossible at present because of the unavailability of convenient hospital facilities. It is planned to expand the present efforts in such a direction in the new Clinical Center quarters, and professional personnel here and arriving later have been recruited with such expansion in mind.

The staff and facilities of the Laboratory of Cellular Physiology, on the other hand, constitute an ideal counterpart to the former group since problems of a particularly technical or biochemically involved sort can be studied collaboratively with full advantage being taken of the specialized instrumentation and training of the Cellular Physiology group. The latter group is primarily interested in the fundamental biochemical mechanisms of cell metabolism with emphasis on energy production and utilization of such energy for biosynthetic processes.

Over-all research in both laboratories is primarily concerned with a limited number of major biological phenomena, but a flux of exploratory work is constantly in progress for the purpose of delimiting new and possibly important areas for study, and for the examination of side developments of major programs which appear to merit special attention.

Laboratory of Metabolism

Studies on the Metabolic Defect in Atherosclerosis. Professional staff: R. K. Brown, Edwin Boyle, Joseph Bradgon, Howard Eder, and C. B. Anfinsen.

Earlier studies by Gofman and his co-workers at the University of California suggested that the development of atherosclerotic lesions might be associated with the presence in the plasma of certain abnormal fat-protein complexes, termed lipoproteins. The development of our own research has been predicated on the observation that heparin, long known as an anticoagulant, possesses the ability, upon injection, to decrease or remove the turbidity of plasma due to lipoprotein material. By a combination of biochemical and physical techniques, a system of enzymatic substances has been discovered which appears to be directly concerned with this "clearing" phenomenon and, consequently, to be of considerable interest as a possible normal physiological "check-and-balance" system in the handling of fat. It has been shown that an enzyme in tissue brings about the conversion or activation of a "precursor" protein in plasma to form "clearing factor." This conversion requires the presence of heparin. "Clearing factor" then carries out the transformation of large, abnormal lipoproteins to smaller normal molecules. This latter change is dependent on still another protein factor in plasma, termed "co-protein." The relation of this clearing system to normal fat transport and metabolism and the possibility that deficiencies in one or more of the components may be concerned with the atherosclerotic process are being studied.

The precise nature of the chemical reactions involved is now being elucidated by a combination of purification, isotopic, and physical techniques. Studies have also been initiated to determine whether the "clearing" system is under active control by hormonal agents and whether aberrations in the fat metabolism of individuals suffering from a variety of metabolic diseases are related to the activity of this system.

The Study of Metabolic and Pathological Disturbances Induced By Nutritional and Endocrine Deficiencies. Professional staff: James H. Baxter and Judson J. Van Wyk.

(A) Renal injury due to choline deficiency has been studied in an effort to determine some of the mechanisms involved and the factors which might influence the injury. It has been found that aureomycin, of a number of antibiotics tested, protects most effectively against such renal injury. This effect appears to be due to the antibiotic itself and not to contaminants or substances produced or accumulating due to its presence in the animal.

Decapsulation of the kidney also protects. This effect may be due primarily to the resulting decrease in intrarenal pressure and suggests that decapsulation protects against secondary disturbances (e.g. edema) rather than primary ones due to the choline deficiency.

Dibenamine, which induces both adrenergic blockage and "alarm reaction," also protected partially against choline-deficiency-induced renal damage. Cortisone and thiouracil were also partially effective.

Work on choline deficiency is now being concluded.

(B) Dr. Baxter and Dr. Van Wyk have continued their previous studies on the effects of copper deficiency in dogs. Their evidence suggests that a specific change in the morphology in blood and bone marrow results from such deficiency and that this change is not directly related to the usual iron deficiency syndrome. These preliminary observations are being examined from the standpoint of possible metabolic changes or deficiencies induced by the copper lack. Preliminary studies have demonstrated that neither ascorbic acid oxidase nor polyphenol oxidase, known copper-containing enzymes, are altered in activity or amount. Tyrosine metabolism is also normal in such deficient animals.

Dr. Baxter proposed to continue these basic studies on copper deficiency at both the enzymatic and metabolic levels. He has also begun studies on experimental nephrosis involving the induction of this state of antikidney tissue antibodies. These latter studies are of particular interest since they will furnish an important tool for collaborative examination of the lipoprotein "clearing factor" problem described above, since marked lipemia is an early feature of such nephrosis. Thus, plasmas from experimentally nephrotic animals can be examined for changes in the enzyme pattern of the clearing system during the development of lipemia.

Laboratory of Cellular Physiology

Studies on the Biosynthesis of Proteins. Professional staff: C. B. Anfinsen, D. Steinberg (now on active duty at Carlsberg Lab., Copenhagen), M. Flavin, R. Hendler, M. Vaughn, and R. Redfield.

During the past 2 years a series of studies have been initiated and partially completed to determine the nature of some of the late steps in the biosynthesis of protein molecules. Specifically, the group above has attempted to determine whether proteins are synthesized by a "template" type of mechanism from free amino acids or whether the over-all process is one proceeding in a discrete, stepwise fashion involving the formation of intermediary fragments of a peptide nature.

Insulin, ribonuclease, and ovalbumin have been prepared by in vitro incubation in the presence of a labelled precursor amino acid. After isolation and purification of the protein under study, samples of this amino acid have been isolated from different structural areas of the protein molecules. It has been found that the specific radioactivity of these samples varies from place to place in the protein structure. These results are compatible with a synthetic mechanism involving intermediates and not with a "template" process, since the latter would lead to uniform labelling.

A general hypothesis has been developed in which peptide fragments, synthesized from amino acids by cellular enzymes, serve as precursor fragments for many different proteins. In line with this suggestion, Dr. Redfield is carrying out studies to determine the exact chain structure of ribonuclease, much as Langer has done for insulin. Should common, recurring sequences be formed upon comparing insulin and ribonuclease structures, it is planned to study the incorporation of such sequences, labelled isotopically, into these and other proteins simultaneously. Dr. Flavin has recently shown that the sequence, - cysteine-glycine - occurs in ovalbumin as it does in insulin, and studies are under way to determine whether or not glutathione (γ - glutamyl-cysteine-glycine) can act as a primary donor of this sequence to both ovalbumin and insulin.

The over-all activity of this group is a long-range one on a phenomenological problem of general interest in numerous metabolic and clinical areas. Dr. Steinberg, upon his return in July to the NIH, has planned to extend some of our basic findings to humans, using N^{15} tracer techniques as a tool for studying peptide pools and synthetic rates in normal and endocrinologically disturbed individuals.

Cellular Energy Production and Biosynthetic Mechanisms. Professional staff: E. R. Stadtman, W. W. Kielley, M. Horning, T. Stadtman, S. Korkes (Visiting Scientist), and C. B. Anfinsen.

Although each of the above listed investigators is carrying out essentially independent research, their studies are linked, through common interest and methodology, to the general problem of cellular biosynthetic mechanisms.

Frequent collaborative experiments on problems of mutual interest to two or more members of this group have been of particular value to the overall program.

(A) Dr. E. Stadtman (with Dr. S. Korkes) has continued his fundamental studies on the enzymatic mechanisms of fatty acid oxidation and synthesis. Using a particularly suitable enzyme source, extracts of *Clostridium kluyveri*, he has delimited several of the central steps in the metabolism of acetic acid and its homologues. The enzymatic synthesis of acetyl-coenzyme A has been accomplished. The role of this "activated 2-carbon" fragment and of CO-A itself in various transfer reactions has been studied and appears to be of central importance in fatty acid oxidation and synthesis. Dr. Stadtman's research efforts were recognized nationally during the past six months by the award to him of the Paul-Lewis prize, given each year to the outstanding American enzyme chemist under the age of 40.

(B) Dr. Kielley has concerned himself primarily with the elucidation of the mechanism of high-energy phosphate (utilizable energy) bond formation during cellular oxidation. This difficult and fundamental problem is of prime importance to all workers in the field of biosynthetic mechanisms, since it concerns itself with the process from which most, if not all, energy for life processes is derived.

He has demonstrated that this process of "oxidative-phosphorylation," carried out by cellular particles called mitochondria, is closely dependent upon the adenylic acid-adenosine polyphosphate system and that deleterious agents such as dinitrophenol may act through the creation of an imbalance in this system. In addition to these studies, he is at present examining, in collaboration with Dr. E. Stadtman, the possible role of coenzyme A and related compounds in the phosphorylating system.

(C) Dr. Horning has prepared C^{14} labelled cholesterol by organic synthesis, labelled in both the C-26 (side chain) and C-4 (ring A) positions. These materials are designed for use in studies on the biological oxidation of cholesterol. It is planned to examine cellular and cell-free extract systems for their ability to convert this common tissue material to bile-acids and to compounds of hormonal interest (e.g. sex steroids, cortisone, etc.). Preliminary experiments have shown that the side chain terminal carbon is removed enzymatically by a system composed of washed mitochondria, a soluble liver enzyme, DPN, adenylic acid, and nicotinamide. This finding now permits enzyme purification and the elucidation of the mechanism of this important cellular reaction.

(D) Dr. T. Stadtman has concluded most of her studies on cholesterol oxidation by microorganisms. Although both wet and dried cells oxidize cholesterol rapidly, the preparation of cell-free extracts capable of performing such oxidation has met with little success. In the absence of such a system, the chance of determining intermediates in the over-all process is small, and these studies are therefore being continued in the mammalian system described above. Dr. Stadtman's accumulated experience in this field will be of great aid in these latter studies. Her major effort, at present, is directed toward the study of 1-carbon metabolism in organisms which can live on 1-carbon compounds exclusively. Recent experiments have demonstrated the occurrence of a number of 1-carbon transformations in these organisms which constitute an ideal cellular preparation for this investigation. An additional feature of interest is the very high level of vitamin B_{12} in these cells, suggesting that the involvement of this substance in 1-carbon metabolism, often postulated but never shown, may be studied here in an especially profitable way.

Laboratory of Cardiovascular Hemodynamics

This laboratory has remained at about the same size during the past year and, pending the opening of the Clinical Center, has remained associated with the Department of Medicine of the New York Hospital and Cornell University College of Medicine.

Studies in Hypertensive Vascular Disease. The clinical facilities provided at the New York Hospital have afforded an opportunity to examine certain features of the natural history of hypertensive vascular disease. In all of the studies where such correlations are possible, the relationship of more general problems to the behavior of the peripheral capillary bed is studied by the special techniques which Dr. R. E. Lee is exploiting. A broad survey of blood pressure in school children on the East Side of New York City has been undertaken, and early results indicate an incidence of about five percent of hypertension in these children. It is hoped that this group who show a rather wide spectrum of racial and ethnic backgrounds and of dietary habits will be amenable to long-term follow-up, and that serial examinations will give insight into factors important in the development of hypertensive vascular disease.

A description of the behavior of the capillary bed in patients suffering from Cushing's syndrome, pheochromocytoma, multiple myeloma, diffuse vascular disease, vascular headache, and toxemia of pregnancy, has been started. Although the case material does not permit far-reaching conclusions because of limited numbers in the study, a preliminary estimate would indicate that some of these diseases are associated with rather distinctive behavior in the conjunctival capillary bed. These studies may well provide a clue to the mechanism responsible for hypertension in the various clinical syndromes studied.

The opportunity to evaluate the correlation between the behavior of the peripheral vascular bed and the response to treatment with low sodium diets, cation exchange resins, and hexamethonium in hypertensive patients has been exploited.

The peculiar behavior (with a marked pressor response) of hypertensive patients to the stimulus of breathing gas mixtures containing a high partial pressure of carbon dioxide is under study. This pressor response is being compared to the cold pressor test in a series of patients with essential hypertension.

Basic Studies of Peripheral Vascular Phenomena. On a more basic level, studies on hemodynamic behavior of the golden hamster have been undertaken. The normal range of blood pressure has been established, and the magnitude of its response to pressor and depressor agents has been documented. The arterioles of the hamster cheek pouch constitute a readily accessible area in which peripheral vascular phenomena can be observed and modified by highly precise micromanipulative instruments. The relationship between the intensity of direct electrical stimulation and degree of contraction of the vessels in this pouch is under study. The reactivity of these vessels to topically applied pharmacodynamic agents in graded doses is also being scrutinized.

In the general area of the role of nutrition in peripheral vascular phenomena, several programs of interest have evolved. An extensive study of vitamin C deficiency in the guinea pig has shown that the scorbutic pig cannot maintain adequate arteriolar activity and also that surviving kidney slices from these animals are incapable of producing VEM. Tetrazolium chloride reduction by the adrenal glands of these animals is increased, and the effect of various substrates and enzyme inhibitors on the reduction of tetrazolium by the adrenals of both normal and scorbutic pigs has been studied. It has also been found that administration of folic acid to these animals postpones the onset of scurvy but does not affect the capacity of surviving kidney slices to produce VEM, nor would diets high in sodium restore the capacity to make VEM. It was also noted that administration of folic acid to normal guinea pigs resulted in a significant incidence of hypertension and kidney lesions after about three weeks. Hypertension did not occur when large amounts of choline were added to the diet. Experimental hypertension in the rat was not modified by low protein diets.

Plans for the future will proceed along lines of the utilization of the special techniques for observing peripheral vascular phenomena that have been acquired by these investigators in both normal human and animal subjects and in naturally occurring vascular disease of man as well as in experimentally induced cardiovascular disease in animal preparations.

Laboratory of Kidney and Electrolyte Metabolism

Work in this laboratory (Robert W. Berliner, Chief) has been concerned largely with the study of electrolyte metabolism, covering a range from basic investigations of the mechanism of electrolyte transport across isolated membranes, through studies of electrolyte distribution in tissues and of mechanisms involved in the regulation of electrolyte metabolism by the kidney, to more applied studies of the nature of the disturbances leading to the retention of fluid and electrolyte in experimental conditions analogous to cardiac failure.

Anion Transport Across the Gastric Mucosa. In order to understand the mechanisms involved in the movement of electrolytes across living membranes it is necessary to be able to study instances of such transport where direct measurements and control of variables are possible. The isolated mucosa of the frog stomach contains a system for the transport of ions which is well suited to such study. Dr. C. A. M. Hogben has been examining this preparation using the approach devised by Ussing. By the use of radioactive labelling, measurement of electrical gradients, and fixing of the electrical potential at any desired level, it is possible to determine which ions move across the membrane at rates determined by the electrochemical gradient (passive movement) and which do not (active transport). It has been found that chloride is actively transported by this system and that the net chloride transport is equal to the electrical current flow plus the hydrogen ion secreted. Working from the hypothesis that chloride transport is some sort of an anion exchange, experiments are under way to identify the partner anion. As part of these studies the effects of CO_2 and of various foreign anions added in concentrations higher on one side or the other have been examined. The data are not yet sufficiently complete for definitive interpretation. These studies have been greatly facilitated by apparatus designed by Dr. R. L. Bowman (Laboratory of Technical Development).

Methods for the Evaluation of the Distribution of Electrolytes in Tissues. Since the electrolyte composition of cell fluid must be deduced from the analysis of tissues containing variable amounts of extracellular fluid, methods for quantifying the volume of this extracellular space are essential to definitive measurement of cell composition. Many investigators have abandoned the classical assumption that all chloride is extracellular (at least in muscle) in the light of the much smaller volume of distribution of inulin. Because of paradoxical results obtained by several investigators using the usual techniques for the measurement of inulin space, Dr. Ernest Cotlove has undertaken a study of the kinetics of the distribution of inulin and of sucrose in rat muscle and tendon. Using a technique for the continuous infusion of the intact, unanesthetized rat which he has devised (and which should find wide usefulness in other studies). Dr. Cotlove has examined the change in the ratio of inulin (or sucrose) space to chloride space in muscle. Two phases are observed and are independent of exercise: A rapid early phase, the saccharide space reading 80 to 85 percent of the chloride space in 2 hours; and a very slow second phase with a ratio of 0.93 at 15 hours and 0.98 (sucrose) at 45 hours. Since even with prolonged infusion there is no tendency of the saccharide space to surpass that of chloride it is unlikely that the former penetrates cells and it seems probable that not more than 5 percent of the muscle chloride is intracellular. In an attempt to explain the extremely slow late phase of distribution a study of intercapillary distances in muscle (20-200 μ, average 50) and tendon (500-4000 μ, average 800) has been made. These taken together with the equilibration data have been used with the equations of A. V. Hill to estimate the diffusion coefficients of these saccharides in these tissues. Values of the order of 1 percent of those in water are estimated to obtain. Preliminary in vitro results with strips of rabbit tendon indicate values of similar magnitude. The slow phase of distribution in rat muscle and tendon is presumed to be due to restricted diffusion in poorly vascularized tissue.

As incidental developments in this work, a greatly improved technique for the measurement of renal clearances in the rat has been devised and the reported excess of creatinine clearance over inulin clearance has been confirmed. An alkali-labile, nonreducing fraction has been found in all commercial preparations of inulin.

Renal Mechanisms for Electrolyte Transport. Several aspects of the processes involved in regulation of the electrolyte content of the body have come under study. The mechanism by which acid-base balance is stabilized by acidification of the urine has been examined, particularly in its relationship to potassium metabolism. This mechanism, an exchange of hydrogen ions for sodium ions, has been shown by Dr. R. W. Berliner, Dr. T. J. Kennedy and Dr. J. Orloff to be in competition with a similar process which exchanges potassium ions for sodium ions. Further support for this thesis has been obtained by the demonstration that lithium salts, known to increase potassium-sodium exchange, also inhibit hydrogen ion secretion. The proposal of Cooke et al that the alkalosis of potassium-depleted animals is initiated by a transfer of hydrogen ion into cells has been confirmed in this laboratory by studies in nephrectomized, potassium-depleted rats, whose alkalosis disappeared on infusion of potassium but not sodium salts. A shift of the balance between hydrogen and potassium secretion by the renal tubules is apparently responsible for the maintenance but not the initiation of the alkalosis. Studies are planned which may ascertain whether the competition is dependent upon an obligatory inverse relationship between the concentration of hydrogen and potassium ions within cells.

Because of the apparent identity of the mechanism by which potassium and hydrogen ions are exchanged for sodium and because the hydrogen exchange ions are exchanged for sodium and because the hydrogen exchange process has been found to be physiologically more extensive than previously believed, the hypothesis has been advanced that all sodium reabsorption is by this transport mechanism. The nature of the anion movement which accompanies this transport has therefore come under consideration. Studies using foreign anions to examine the hypothesis that chloride transport is likewise an ion exchange mechanism have been instituted but have made only very slight progress because of methodological difficulties.

The excretion of ammonia is one of the most important processes involved in stabilization of acid-base balance. It has seemed desirable to investigate whether the process involves a transport of ammonium ions or diffusion of ammonia in the free state and to examine some of the factors influencing the rate of ammonia production. Certain basic organic compounds, highly concentrated within cells, are excreted, like ammonia, at rates dependent on the urine pH. From the hypothesis that the process involved is simply one of distribution equilibration between urine and cell with the electrochemical potential the same in urine and cell, such a compound might serve as an internal reference standard for eliminating the effect of those factors affecting compound and ammonia similarly. Studies by Drs. Orloff and Berliner with SN 8439, a derivative of q-aminoacridine, with a pKa (8.9) close to that of ammonia (9.2), have shown this compound to be satisfactory in that variations in excretion rate of acridine and ammonia over a ten-fold range produced by infusion of bicarbonate do not change the proportions of each excreted. Changes in excretion produced by means thought to increase ammonia formation (administration of precursors) increase ammonia excretion disproportionately, and to raise cell pH (inhibition of carbonic anhydrase, administration of potassium salts) decrease ammonia excretion disproportionately. The preliminary data are in accord with the hypothesis that the rate of production of ammonia is inversely related to cell pH and that increased ammonia formation tends to decrease intracellular hydrogen ion concentration:

Renal and Hormonal Factors in States Associated with Ascites and Edema. Many of the clinical manifestations associated with cardiac failure can be attributed to accumulation of an excess of fluid in the body. Although retention of sodium by the kidney is the essential final step leading to this accumulation, elucidation of the chain of events involved, from initial stimulus to modification of the transport mechanism, remains a major problem. Dr. J. O. Davis and Dr. D. S. Howell have been using metabolic balance studies to examine the role of certain endocrine organs and of the kidney in the sodium retention which leads to accumulation of fluid in the peritoneal cavity in dogs with certain experimentally produced abnormalities of the cardiovascular system. These studies were begun with the investigation of constrictive pericarditis induced by placing cellophane in the pericardial cavity. In all observable features associated with the fluid retention, the far more reproducible lesion produced by a constricting band on the thoracic portion of the inferior vena cava has been found essentially identical with that of constrictive pericarditis. The inferior vena cava preparation has therefore been used in the more extensive studies involving removal of endocrine organs. Studies of mitral stenosis produced by a wire progressively tightened around the mitral valve ring have been instituted in order to further test the validity of applying information gained from the study of constriction of the inferior vena cava to cardiac failure in dogs and thence to the clinical disorder.

Although previous work by Dr. Davis and Dr. Howell had shown that depression of the glomerular filtration rate under basal conditions was not involved in the fluid retention, the variability of this function in the dog has necessitated further examination of the problem. Since under basal conditions the normal dog excretes no salt, but puts out the major portion of that ingested during a period of elevated filtration rate following meals, it has been necessary to exclude the possibility that such a rise fails to occur in the dog accumulating fluid. In the dog with constriction of the vena cava the rise in filtration rate does occur but is not accompanied by increased salt excretion. The factor of glomerular filtration has therefore been excluded and the retention of sodium can definitely be attributed to enhanced transport by the renal tubules.

Enhancement of this transport mechanism with evidence of factors leading to sodium retention elsewhere in a decreased output of sodium and increased excretion of potassium in the stools has directed attention to the adrenal glands since certain adrenal hormones are known to exert such activities. Removal of the adrenals resulted in rapid disappearance of the abnormal fluid collections. Dogs so treated could be maintained in good health with doses of adrenal hormones of the size required to maintain adrenalectomized dogs without the constricting bands, but did not reaccumulate fluid unless given large excesses of desoxycorticosterone.

The dogs with marked sodium retention suggestive of adrenal hyperactivity do not show evidences of overactivity in other spheres under the influence of the adrenals. If the electrolyte effects are to be attributed to the adrenals, as suggested by the findings cited above, such activity of the adrenals must be independently mediated. Studies of the effects of ACTH and cortisone, and of hypophysectomy and adrenalectomy have been done to investigate this possibility. It has been shown that ACTH or cortisone, rather than causing retention of salt in the dog, lead to negative sodium balance, presumably because of a predominating elevation of glomerular filtration rate. Hypophysectomy in the dog with constriction of the vena cava does not lead to loss of fluid accumulation, although the inverted sodium-potassium excretion ration in the feces does disappear. The latter is not re-established by administration of ACTH. Present work is proceeding on the hypothesis that the immediate stimulus to excessive sodium transport by the renal tubules is one or more salt-active hormones secreted by the adrenals, this activity being induced by some stimulus not mediated by the effects of pituitary adrenocorticotropin.

Laboratory of Physiology and Pharmacology of the Autonomic Nervous System

Operation of this laboratory began in July 1952 when Dr. Neil C. Moran reported to the Heart Institute and was assigned to the Department of Pharmacology, Emory University School of Medicine, to work under the general guidance of Dr. Arthur P. Richardson, Chairman of that department. With the opening of the laboratories in the Clinical Center in the latter part of 1953, the staff will be increased.

Screening of Drugs for Their Actions on Cardiovascular Phenomena. Dr. Moran has endeavored to establish at an early stage a highly stylized screening procedure whereby pharmacological agents can be quickly assayed for their effectiveness to modify such cardiovascular phenomena as blood pressure, the electrical response of the myocardium, and the automatic nervous system control of cardiovascular function. In his screening procedure, the unknown drug is compared to the prototypes of compounds possessing known pharmacodynamic activity. In addition, the relationship between dosage, activity, and toxicity is established in a general sort of way. The screening procedure, as it has worked out in practice, will allow one to decide from the data of two comparatively simple experiments whether a drug possesses characteristics sufficiently greater than commonly employed agents to warrant further studies.

Using this screening procedure, Dr. Moran has examined a large number of compounds sent him by the Laboratory of Chemistry of Natural Products and by the Squibb Institute for Medical Research. Many of these drugs possessed hypotensive activity, others were adrenolytic, others produced nicotine-like effects, some possessed anti-cholinesterase activity, etc. Alkaloids from plant extracts, largely uncharacterized chemically, have been screened and an impressive number have shown capacity to modify cardiovascular function to greater or lesser degree. Some of these will undergo further chemical fractionation and characterization and will be reexamined when they are more highly purified. In the latter class is the material from Rauwolfia Serpentina Bentham. It seems almost certain that the study of compounds derived from natural sources will eventuate in the discovery of a large number of agents potentially useful in the management of cardiovascular disease. Moreover, the unique facilities of the Heart Institute for testing as well as for chemically characterizing these compounds should result in a significant advance in our understanding of the relationship between the chemical structure and the pharmacodynamic activity of these agents. Such understanding will provide the groundwork for insights into the intimate biochemical processes of the normal as well as the diseased cell and organ.

The wide clinical interest in the problem of resistance to the adrenolytic agent Regitine led Dr. Moran to undertake a study of the mechanism for the development of this resistance, using the dog as an experimental animal. Unfortunately no evidence for the development of such resistance in this species could be obtained.

Laboratory of Technical Development

The general purposes of this laboratory (Bert R. Boone, Chief) are the development of new instruments and methods leading to new investigative technics in basic and clinical cardiovascular research. This requires the following areas of activity: (1) basic investigations in physical, biophysical, and biochemical principles; (2) development of instruments and methods for specific purposes; (3) modifications on existing instruments to extend their applications; (4) collaboration with other NHI laboratories in developing instruments and methods for their researches; and (5) consultation with Institute and extramural investigators concerning the best approach for implementing their various problems.

Development of an Improved Method for Determining Freezing Point Depressions in Aqueous Solution. The purpose of this project, conducted by Dr. Robert L. Bowman, is to improve the methods of determining freezing point depressions. The method consists of utilizing a vortex tube refrigeration system together with an AC thermister bridge for reading temperature differences. Various designs of vortex tube heat exchangers have been tested, and an efficient, compact system for cooling and freezing the same has been devised. A thermister bridge has been developed to read temperature differences of .0018° C per scale division. Features of this bridge are the elimination of the expensive high sensitivity galvanometer and Wheatstone bridge, in favor of electron-eye-tube indication and a ten-turn, 1000 division Helipot (expanded scale) bridge. Freezing point depressions have been determined in a number of standards and unknowns to test capabilities and speed. Performance data indicate the final instrument promises to be an improvement in the art of determining freezing point depressions. The sensitivity of the thermister bridge system is being increased and made more flexible so that freezing points of other than water solutions may be determined. Also improvements in the cooling chamber and stirring suspension continue. A testing program has shown that experienced or inexperienced technicians utilizing the instrument can quickly be shown to make ten freezing point determinations per hour good to less than 2 percent accuracy.

Development of Ultraviolet Photofluorometry to Include Measurement of Ultraviolet Emission. This project, conducted by Dr. Robert L. Bowman, is investigating the extent to which substances having absorption bands in the mid to far ultraviolet exhibit fluorescence in the ultraviolet region. A fluorescent spectrum scanning and recording system has been developed, tested, and proved to have good sensitivity and resolution to survey compounds for fluorescent activity in the ultraviolet and to select source and emission filters for filter system photofluorimeters. Progress has been slowed during past six months due to increased work on other projects. Work will be resumed to extend the range and sensitivity of the apparatus and to examine the fluorescent spectra of compounds of biochemical interest to determine the value of these spectra in relation to characterization and quantitation.

Function Generator and Fourier Analyser. The general purpose of this project, conducted by Mr. Frank Noble, is to provide means for obtaining quickly an analysis of the frequency, amplitude, and phase relationships of the harmonic components which make up a given biological tracing. The methods employed are electronic and consist of constraining the cathode-ray beam to follow the outline of a shadow-graph of the desired waveform. A cathode ray frequency analyser displays the frequency content, which is photographed by a rapid process camera. Frequency analysis of complex biologic waveforms is important to determine the physical characteristics required in an instrument which will be used to measure the particular phenomenon. Concerning progress, a satisfactory Function Generator - Fourier Analyser combination has been devised and checked by the use of test curves of known frequency-amplitude content. Analyses of typical sample biologic curves are now in progress. Circuits for determining phase have been designed and partially constructed. Work will continue towards the perfection of the apparatus which will provide rapid analysis of both frequency-amplitude and phase of the components of a given biological tracing. An interesting sidelight may be the use of this method for the precise classification of such clinical curves as the electrocardiogram, pressure pulse curves, etc.

A Carrier-type Electrokymograph. The purpose of this project, conducted by Mr. Frank Noble, is to provide a true zero frequency response amplifier for the electrokymograph, to improve upon the amplitude-frequency response of the instrument, and to provide either linear or logarithmic output proportional to the input signal. The method consists of amplification of the alternating current component of the X-ray beam to a high level, with subsequent demodulation and direct-coupling to an appropriate recording device. The importance of such an instrument will be the ability to measure the X-ray density or thickness of an object such as the chest or heart within the chest. In essence it is an X-ray photometer. To date the design has been worked out, an amplifier constructed, and partial testing has been done. Further work and testing will be continued upon completion of stabilization of the X-ray source. The device may become of use in clinical investigation for recording the thickness of the ventricles in systole and diastole and possibly in estimating stroke volumes.

Resistance--Capacitance Filter for an X-ray Machine. The purpose of this project, conducted by Mr. Frank Noble, is to develop filters for the high voltage and filament supplies of an X-ray machine in order to provide constant intensity X-rays for use with the conventional electrokymograph. A constant intensity X-ray source will allow the removal of filters in the electrokymograph which are required to eliminate the 120-cycle ripple in the output of conventional X-ray equipment, and which have a deleterious effect upon the high frequency response of the instrument. The filters have been designed, constructed, and installed on a Picker fluoroscope. A special line voltage regulator is now being installed, following which appropriate testing of the entire system will be done.

Instrumentation for Maintenance of a Circulated Isolated Dog Kidney. The purpose of this project, conducted by Dr. R. L. Bowman and Dr. T. J. Kennedy (Laboratory of Kidney and Electrolyte Metabolism), was to develop and record the condition of the circulation of an isolated dog kidney so its handling of water and electrolytes can be studied. In cooperation with Dr. Kennedy and Dr. Winton (of England) an all plastic blood pumping system was constructed. Also a blood pressure regulating system was developed, and various methods for sensing and recording pressures, flow, and temperature.

The Use of Diodrast in Electrokymography. The purpose of this project, conducted by Mr. Frank Noble, Dr. B. R. Boone, and Dr. Richard Bing of Johns Hopkins Hospital, were (a) to determine the feasibility of injecting diodrast into a right ventricle by catheterization and observing its concentration in the pulmonary artery by the electrokymograph, and (b) to determine the feasibility of differential diagnosis of certain shunts in congenital heart disease, by observing time of appearance of diodrast in the aorta using the electrokymograph. Under part (a) several patients were tested, and diodrast concentration curves recorded. It was found impracticable if not impossible to accurately quantitate the system to obtain stroke volume and cardiac output. Under part (b) preliminary work showed that such small quantities of diodrast as 5 cc. could be detected with respect to time of appearance in the aorta. Dr. Bing left Johns Hopkins Hospital before further work could be done, and work was temporarily suspended.

Clinic of General Medicine and Experimental Therapeutics

This clinic (Luther L. Terry, Chief), organized approximately 3 years ago, is located at the Public Health Service Hospital in Baltimore, Md., and has collaborated with the Division of Hospitals in conducting an investigative and patient-care program in that institution. In conducting the medical care program in cardiovascular diseases, the group has gained access to a large number of patients for research studies. The quantity and quality of the clinical material which was available through the routine beneficiaries of the Public Health Service has been supplemented with special study cases when desirable cases became available through other sources.

In establishing the Clinic at the Baltimore Hospital it was the plan that the group would be gradually developed into a smoothly functioning clinical research team to assume this responsibility in the Clinical Center when facilities became available there. During the past eighteen months this development has been gradually accomplished so that the Clinic is now ready to move into the Clinical Center as an operating unit. The final phase of development has occurred within the past three months when the personnel of the Clinic has been formally organized into three research teams (Sections) each of which is headed by one of the three senior investigators within the Clinic. The Chief of the Clinic also acts as head of one of the Sections (Experimental Therapeutics). The other two Sections are under the direction of Dr. Robert P. Grant (Cardiodynamics) and Dr. Frederic C. Bartter (Clinical Endocrinology). This organization affords each of the research teams the desired amount of authority and responsibility necessary to the conduct of research.

It is anticipated that in moving to the Clinical Center within the next few months the Clinic will continue its research program in much the same manner as it has in the past. Facilities in the Clinical Center should allow more intensive investigation of some of the problems and the Clinic should benefit as a result of closer contact with other laboratories of the Heart Institute. Some of the present projects will have been completed by the time of the move but protocols of other projects are under preparation at this time and the Clinic expects to utilize the new facilities to the greatest extent.

Below is a description of the significant research projects which have been pursued during the past eighteen months. For purposes of organization the projects are listed and described under the head of the Section in which the principal assignment of the project has been performed. However, it should be clear that many of the projects have crossed team lines when interest and abilities have so dictated. In addition, it will be noted that several projects are listed under the heading "Surgery." Dr. Converse Peirce, 2nd, has been assigned to the Clinic for operational purposes until the Institute's Clinic of Surgery is more fully organized. He has served as an integral portion of the research team and has been of great value to the group in rendering medical care.

Section of Clinical Endocrinology

The Action of Parathyroid Hormone. For several years Dr. Frederic C. Bartter has been interested in the physiology of the parathyroids and the mechanism of action of the parathyroid hormone. During the past eighteen months these studies have been continued with special references to the effect of parathyroid hormone on the tubular transfer of phosphate. Certain changes in "Phosphate Tm" have been observed as a result of anesthesia, the administration of ACTH and parathyroidectomy but the interpretation of these results should await further studies.

The Use of Cation Exchange Resins in the Treatment of Edema. Careful balance studies on a group of patients with edema have been performed by Dr. Leroy E. Duncan, Jr. These studies have shown that the uptake of sodium on cation exchange resins is not related to the oral intake of sodium alone, as has been commonly supposed. On the other hand, he has shown that in an individual patient the sodium uptake of the resin is directly correlated with the amount of edema present and is not affected by the dietary sodium intake until edema has accumulated. This study has considerable practical clinical importance since resins are being used widely in clinical practice without a previous clear understanding of the mode of action.

The Sodium Transport Mechanisms of the Intestinal Mucosa. Dr. Duncan became interested in this subject in connection with his studies on cation exchange resins. He has shown that this transport mechanism is a major factor in the efficacy of treatment with exchange resins and that dinitrophenol will block the transport of sodium against a chemical concentration gradient.

Study of Patients with Low Serum Sodium. Dr. Duncan has been studying a group of cardiac patients with edema of edema-forming tendency and low serum sodium. He is seeking to characterize the metabolic picture in these individuals in order that such patients may be treated more rationally. Results thus far suggest that these patients are homeostatically set so that their serum sodium concentration is low and that displacement from this level is compensated for in a tendency to return to this level. Though this subject is of great importance no clear understanding of the mechanism or its correction has yet been evolved.

Renal Transport Mechanisms: Accumulation of PAH by Rat Kidneys. Dr. Agememnon Despopoulos has been studying renal transport mechanisms particularly as related to glucose and PAH. Earlier studies with dogs failed to show any change in the reabsorption of glucose by renal tubules (tmg) either by insulin or by pancreatectomy. More recently he has studied the active transport of PAH across the renal tubular cell of rat kidney slices in the Warburg apparatus. He has found that the transport of PAH in rat kidney cortex is greater than in the dog or rabbit. The addition of acetate in low concentrations did not affect the mechanism, but in higher concentrations (0.03 M to 0.1M) acetate did inhibit the transport mechanism. He is now planning on extending his observations on this subject to include the effect of hormones on the transport process for PAH.

The Action of Pitressin in Man with Especial Reference to Edema. In this study Dr. Bartter is observing the effects of administration of pitressen in man under varying loads of salt and water. These results are being compared with and without the use of ACTH. The results are yet inconclusive and further observations are being made.

The Excretion of an Ampholyte in Renal Tubular Acidosis. The presence of an unidentified urinary ampholyte in renal tubular acidosis was previously reported by Dr. Bartter (with Dawson, et al). The present study is directed toward the identification of this substance. Certain identifying features of this substance have been established but its exact nature is unknown. The efforts toward identification are in progress.

Section of Cardiodynamics

Electrocardiography. This project, under the direction of Dr. Robert P. Grant, has continued during the past eighteen months. Drs. Harold Dodge and Raymond Murray have collaborated in these studies:

a) One phase of study has correlated the postmortem findings of the position of the heart with electrocardiograms taken during life. A large number of cases have been studied. In substance, this study failed to reveal any marked shift or rotation in the position of the heart with various types of cardiac enlargement. The findings are in sharp contrast to the popular concept, especially as fostered by many electrocardiographers.

b) A second phase of study consists in vector analysis of a large group of electrocardiograms taken on patients before and after proven myocardial infarcts. Hospital records from many institutions in this general area have been made available to the group and the data are being gathered and studied at this time. This promises to be the first adequately controlled study of this aspect of clinical electrocardiography.

c) A third plan of this project is the construction of an electronic analogue of the A-V conduction mechanism. Dr. Grant is working with our consulting electrical engineer, Mr. Carl Eppers. The device is nearing completion, and it is hoped that studies with it may enhance our knowledge of the conduction mechanism of the heart.

The Intraventricular Conduction System of the Heart. Dr. Raymond Murray has been studying the intraventricular conduction system and has proposed a new theoretical approach. The theory involves a discussion of the genesis of the forces responsible for the initial (.04 sec) deflection of the QRS complex on the electrocardiogram.

The Diagnosis of Intracardiac Shunts. Drs. James J. Callaway and Raymond Murray have devised a method of detecting shunts between the chambers of the heart by utilizing nitrous oxide. Intra-auricular defects have been produced in dogs by Dr. E. Converse Peirce and nitrous oxide collection technique has been developed. It is expected that this method will eventually prove more satisfactory than the conventional methods now available. The work is still in the early stages so that no conclusions can be drawn at present.

Architectonics of the Heart. Dr. Robert P. Grant has devised a technique of studying hearts post-mortem which he feels will greatly increase our knowledge of the physiology of the normal and abnormal heart. A large number of hearts have been studied by this three-dimensional technique and evidence indicates that it is superior to the conventional two-dimensional technique. Before further statements are made it will be necessary to review more of the data and obtain a larger number of cases.

Pneumothorax: Study of Gaseous Composition and Rate of Absorption. Dr. James J. Callaway is conducting a systematic study of the composition and rate of absorption of artificial pneumothorax in dogs. Since so little information is available, it is felt that this study would enable one to use therapeutic pneumothorax more effectively and would provide fundamental information regarding the diffusion of gases in man. A few pilot studies have been conducted and methods of collection of gas and other experimental designs have been completed. No significant results are available at this time.

The Effect of Hyperkalemia on the T-wave of the Electrocardiogram. Dr. Robert P. Grant and Dr. Harold Dodge have studied the effect of potassium on the EKG of normal persons, patients with heart disease, and patients with abnormal T-forces as a result of metabolic or hemodynamic factors. It was found that the patients with heart disease did not show any correction of abnormalities of T-forces as a result of potassium. In the presumably normal persons with abnormal T-forces, the abnormalities were corrected. In patients with isolated T-deformities, the deformities were not abolished by potassium. This project has been completed, and the data are being prepared for publication.

Experimental Therapeutics

The Diuretic Action of Alcohol and Factors Influencing Its Magnitude. Dr. William Fritz is collaborating with Dr. E. K. Marshall, Professor of Pharmacology at Johns Hopkins Medical School, on factors affecting diuresis. The diuretic action of alcohol is being investigated with particular attention to possible motivation through the posterior pituitary. No significant results have been obtained thus far.

Mercuhydrin Potentiating Action of Decholin. The empirical observation has been made that decholin potentiates the effect of mercurial diuretics. A group of patients with and without edema were given mercuhydrin and decholin but no consistently potentiating effects could be demonstrated. The subject was not felt to merit further study.

The Hypotensive and Antiarrythmic Effects of Crataegus. It has been reported that tincture of Crataegus oxycantha has a hypotensive effect. Preparation (tinctures and extracts) of both American and European Crataegus were tried in patients with hypertension. No hypotensive effects could be demonstrated, but some of the earlier studies suggested that the substance might have antiarrythmic activity. This hypothesis was tested further in many patients with arrythmias but such effects could not be demonstrated clearly. The results were not sufficiently encouraging to merit further study and the project was terminated. The study was conducted by Dr. Luther L. Terry and Dr. William F. Fritz.

Irreversible Circulatory Failure Following Ligation of the Supradiaphragmatic Inferior Vena Cava. Dr. William F. Fritz studied the mechanism of the sharp and persistent fall of blood pressure in dogs following ligation of the supradiaphragmatic vena cava. The changes were found to be due to the rapid bleeding off into the liver, and sphanchnic vessels and lower extremities. It could be largely averted by ligation of the aorta above the celiac axis or hepatectomy. It is thus felt that the changes described are in fact due to bleeding off and inadequate venous return.

Dynamic Effects of Transfusion and Venesection on the Survival Time of Dogs With Acute Pericardial Tamponade. Dr. Fritz began this project and found that venesection resulted in cessation of circulation at lower levels of intrapericardial pressure than in the dog that had not been bled. Further, it was shown that following transfusion it required a higher intrapericardial pressure for circulation to cease. At this stage of the project Dr. Fritz began his work with Dr. Marshall and was unable to pursue this work further. It is expected that he will resume the work at a later date.

The Effect of Banthine on the Respiratory Mechanics of Asthma. Banthine (a parasympathalytic agent) was studied by Dr. Albert Sjoerdsma and Dr. Harold Dodge for its effect on the bronchospasm of asthma. Following the administration of 50 mg. of Banthine intravenously, seven of eleven patients with asthma showed a "good" response with marked increase in maximum breathing capacity and three-second vital capacity and marked symptomatic relief. Four of the patients showed little subjective or objective response. The results suggest that Banthine and other parasympathalytic drugs may have some clinical usefulness in the treatment of asthma and other clinical states associated with bronchospasm.

Surgery

Artery Grafting (in dogs). Dr. E. Converse Peirce, 2nd, has been working on this project for more than 4 years. Since the technique of placing such grafts was developed in the earlier stages, his work during the past 18 months has been directed toward further work on methods of preservation of grafts and a study of the factors which contributed to the failure of a graft on implantation. Preservation in nutrient media, formalin fixation, and freezing have all been shown as satisfactory methods of preservation of arterial grafts. Artificial grafts have been prepared by eliciting a fibrous tissue reaction about plastic tubes buried in the subcutaneous tissue, and these grafts have been successful in a large percentage of instances. Recent work has shown that arterial grafts contaminated with feces are uniformly failures due to bacterial contamination. Failure occurs in these instances in spite of concurrent administration of large doses of antibiotics (terramycin).

Extracorporeal Circulation. In these studies paired dogs were used, with one animal utilized as a circulatory pump for both animals while the blood was short-circuited around the left side of the other animal's heart in order to maintain a relatively bloodless field for operations on the interior of the heart. It was found that one animal could satisfactorily maintain the circulation for both animals. However, this procedure required a great deal of surgical skill and a large surgical team. It was, therefore, decided to abandon this procedure in favor of an artificial heart pump.

Artificial Heart Pump. A mechanical pump was designed by Dr. Robert Bowman (Laboratory of Technical Development) which would maintain a satisfactory circulation in dogs. It was shown that this pump could be used to short-circuit the left heart providing satisfactory oxygenation could be obtained. A portion of the lung was used in connection with the artificial pump and the left heart was thus made accessible for direct surgical approach to the interior of the heart. This work has real possibilities for application in humans and may greatly broaden the scope of surgery of the heart.

Production of Mitral Stenosis. Mitral stenosis has been produced in dogs by suturing together the leaflets of the mitral valve. However, it has been impossible thus far to produce a degree of narrowing of the valve orifice which will produce the typical dynamic changes of mitral stenosis and yet not be rapidly fatal to the animal. Further work is being pursued towards obtaining this objective by injecting sclerosing substances into the mitral valve and by using a ligature technique which will permit gradual narrowing of the valve opening.

Diagnostic Aortography. For over 2 years Dr. Peirce has been working with methods of visualizing the aorta and its branches for diagnostic purposes. He has perfected the technique of percutaneous aortography which is accomplished by inserting a large needle through the skin into the femoral artery and then threading a plastic catheter through the needle and inserting it to the desired level in the aorta or its branches. X-ray views are then taken after the injection of radiopaque material. This method avoids cut-down on the artery and yet gives excellent results in the vast majority of cases. An exhibit is being prepared at the present time for showing at several medical meetings and several papers have been published on the subject.

Clinic of Surgery

This clinic was first put into operation in August 1952 when Dr. Thomas N. P. Johns joined the staff of the Heart Institute and was assigned working space in the Surgical Hunterian Laboratory, Department of Surgery, Johns Hopkins University and Hospital. With the opening of the Clinical Center in 1953, the staff of this clinic will be augmented to a sizeable degree, but as yet the position of Chief of the Clinic of Surgery has not been filled.

Production of Collateral Circulation in the Myocardium. Dr. Johns' first efforts have been directed at the improvement of surgical procedures for producing collateral circulation in the myocardium. Previous investigators have transplanted various structure such as omentum, muscle, lung, pericardium, and skin from their normal sites into the pericardial cavity and in contact with the myocardium. Their efforts have met with varying degrees of success, but no clear-cut evidence that significant increases in myocardial blood supply attend the procedure has been forthcoming. The fundamental concept still seems sound, and the necessary solutions may well represent technical problems. Dr. Johns has explored extensively the possibility of removing part of the wall of the stomach with intact blood supply and transplanting the extrapolated segment of the stomach onto the myocardium. He has found that the left gastric vascular pedicle is the largest group of blood vessels to the stomach and that a vascularized portion of the stomach wall corresponding to the lesser curvature and the adjacent posterior and anterior walls could be extrapolated with a satisfactory restoration of gastric continuity. When the mucosa is removed from this extrapolated segment, it comprises a pedicle graft with a rich blood supply which can be placed around the heart through an opening in the diaphragm in such a way as to cover the entire ventricular myocardium. His efforts to date have consisted largely in working out technical details of this procedure. The functional effect on the blood supply to the myocardium is now under scrutiny.

Experimental Coronary Thrombosis. Dr. Johns has also undertaken a study of procedures designed at the selective induction of coronary thrombosis in experimental animals. He has found that this lesion can be produced by passing very small amounts of electrical current for a short period of time through the walls of blood vessels. This procedure will enable investigators to study in a more controlled fashion the pathological physiology of coronary thrombosis and myocardial infarction.

Clinic of Gerontology

Nathan W. Shock is chief of this Clinic. The increasing number of elderly people in our population makes it imperative that we find out more about their physiological and psychological characteristics. The planning of effective methods for meeting not only the health but also the social needs of this increasing segment of our population depends on knowledge of their functional capacities. Interpretation of observations on disease states and their early detection in elderly people depends on precise knowledge of similar observations on individuals of the same age in the absence of disease. Similarly, the pressing questions of retirement policies depend on knowledge of the effects of aging on performance capacities. The research program of the Clinic of Gerontology, located at the Baltimore City Hospitals, Baltimore, Md., is directed toward evaluating the physiological, biochemical and psychological aspects of aging.

Since aging is a process, it cannot be evaluated by observations on old people alone. Consequently, observations have been made on human subjects between the ages of 20 and 90 years. In addition, subjects in all age groups have been carefully screened to exclude those with clinically diagnosable diseases that might have an influence on the functions studied.

The research program of the clinic falls logically into four major categories, viz., cardiovascular studies, renal studies, metabolic and endocrine studies, and psychological studies.

Cardiovascular Studies. Dr. Milton Landowne has devised a new technique for measuring the rate of propagation of a pressure wave in intact arteries. By noting changes in the characteristics of a pressure wave as it passes down an artery, important information about the elastic and structural properties of the artery may be deduced. The rate of progression of the experimentally imposed pressure wave increases with increasing intra-arterial pressure according to the equation $V^2=A+Bp+Cp^2$, where V is the velocity and p is the intra arterial pressure. An increase in velocity of an impact wave with age was found only within a limited pressure range. The rate of propagation of experimentally produced impact waves is approximately twice that of the cardiac pulse wave. Because of the preponderance of low frequency components present in the pulse wave as compared with the impact wave, it is probable that the rate of wave propagation is related to the wave form. Instrumentation has been developed which will permit testing this hypothesis. It is possible that the information obtained will permit further analysis of the elastic and structural characteristics of intact arteries. Age differences in the electrocardiographic response to exercise have been found in subjects (age 20-80 years) without clinical signs of heart disease. The aged subjects showed a greater lowering of the ST segment and T wave and a greater shortening of the QT interval during exercise, although there were no significant differences in the resting state. The time course of recovery after exercise also showed significant age differences. In the old subjects, changes in T wave height developed over a longer period of time and the heart rate recovered more slowly. These changes were in the direction observed in patients with demonstrable diminution in cardiac reserve, but were less in degree. (Dr. Milton Landowne and Dr. Harold M. Silver).

Preliminary results indicate a significant reduction in the rate of response of the peripheral vascular system following the administration of heat to the abdomen of older subjects (Dr. Milton Landowne and Dr. Harold M. Silver). Contrary to expectations, the age difference has been more marked in the fingers than in the toes. Further studies on this problem are planned in addition to the studies of frequency and damping characteristics of arteries.

Renal Studies. Dr. John H. Miller has extended the studies on renal function and has obtained the first evidence of age changes in intracellular processes in the kidney. Preliminary results indicate significant age-wise decrement in response to antidiuretic hormone as measured by the maximum $^U/_P$ inulin ratio attained. Neither the time of occurrence of maximum antidiuresis nor the time to recover from antidiuresis change with age.

Incidental to other studies, Dr. Miller has observed an anti-diuretic effect of insulin under conditions of a glucose osmotic diuresis. This antidiuresis was associated with only a very slight decrease in urinary excretion of solutes. The antidiuretic effect of insulin was significantly less when the diuresis was induced by mannitol.

Dr. Donald M. Watkin has found that the maximum rate of excretion of diodrast (Tm) was significantly less than the maximum rate of excretion of

PAH (Tm) at all ages and that the slope of the regression of Tm on age was greater for Tm PAH than for Tm diodrast.

Work for the coming year will include further assessment of age changes in the level of distal tubular function of the kidney by observing the changes in urine flow and solute excretion following osmotic loading in hydropenic subjects, as well as a comparison of transport mechanisms for PAH and diodrast in older subjects.

Metabolic Studies. The problems of nutrition in the ages have great practical implications. The studies of the clinic have been devoted primarily to the assessment of calcium and nitrogen metabolism in older subjects, utilizing controlled metabolic balance methods. These methods require chemical analysis of all foods as well as urine and stools for the evaluation of dietary factors. The patients must be kept under constant supervision with precisely weighed diets for long periods of time if reliable results are to be obtained. Consequently, studies of this kind are extremely tedious and slow in progress. However, studies on calcium and nitrogen metabolism have been completed which show that in the presence of high protein intakes older subjects are able to store significant amounts of calcium when adequate amounts are present in the diet. Approximately 850 mg. of calcium per day was adequate calcium equilibrium in normal aged males. One patient with definite osteoporosis was unable to retain calcium even at high intake levels in the presence of a positive nitrogen balance. The other subjects showed increasing calcium storage with increasing amounts of calcium in the diet. In addition, it was found that all the aged subjects were able to store phosphorous, potassium and nitrogen (2 to 5 gm. per day) on the high protein diets given (approximately 90 gm. protein per day). Thus, there is good evidence that with an optimal diet the aged subject can form new tissues. Further studies on the effects of steroids and dietary alternations on calcium and nitrogen storage are planned for the coming year. (Dr. N. W. Shock, Dr. Morton Bogdonoff and Dr. Donald M. Watkin)

Other nutritional characteristics of aged subjects have been reported by Dr. Donald M. Watkin who found that old subjects excreted a much smaller proportion of an intramuscular injection of vitamin B12 than did young and middle aged subjects. Further studies on the utilization and excretion of vitamin B12 are planned in collaboration with Dr. Bacon Chow of the Johns Hopkins University School of Hygiene and Public Health.

Normal values for basal oxygen consumption have been extended to include subjects between the ages of 65 and 90 years (Mr. Marvin J. Yiengst). A progressive decline in oxygen consumption per unit of body size was found. However, when a correction for body fat and other nonmetabolizing tissue is made, there is no significant decrement in the rate of basal oxygen consumption with age. Other studies on age changes in respiratory metabolism and function are contemplated.

Estimates of age changes in capacity for physical work have important implications for determining retirement policies in industry. This problem is being attacked at a fundamental level by studying age changes in the metabolic and cardiovascular response to exercise. It has been found that the oxygen required for a standard amount of work is not significantly different for old and young. However, the older subjects must increase their ventilation volume approximately twice as much as young subjects in order to maintain the oxygen intake at the level required for the exercise administered. In addition, the rate of recovery of oxygen consumption and ventilation volume following short periods of exercise is significantly slower in old subjects than in young. Preliminary results indicate that measurements of ventilation volume may serve to distinguish young and old subjects as well as measurements of oxygen consumption or carbon dioxide production. Further experiments are planned to determine the feasibility of utilizing this technique as an index of physiological age and performance capacity. (Dr. N. W. Shock, Mr. Arthur H. Norris and Dr. Joseph A. Falzone)

Psychological Studies. Investigators on the psychological aspects of aging have indicated a slowing of speed of performance in a variety of responses. In order to isolate the physiological aspects of this reduction in speed, measurements of the speed of conduction of a nerve impulse were made. A significant slowing of conduction rate in the ulnar nerve was found over the age span of 20 to 80 years (Mr. Arthur H. Norris). Although statistically significant, the reduction in speed of conduction is not sufficient to explain the total slowing in psychomotor responses which has been found. Other studies involving measurements of coordination of muscle groups are planned.

It has also been found that older subjects maintain a more uniform rate of performance in a repetitive task than do young subjects. Although young subjects show a higher rate of performance when beginning a task, their speed falls rapidly. The old subjects work at a slower rate, but maintain the performance. These experiments have used relatively short durations of work where fatigue is not a major factor. (Dr. N. W. Shock and Mr. Jack Botwinick)

Preliminary results indicate that older subjects are more sensitive to a series of successes or failures than are young subjects. (Dr. N. W. Shock and Mr. Raymond Tiexiera)

Tests of performance on a wide variety of mental tasks has shown that older individuals show very little reduction in performance in tasks that are utilized in their daily life. This finding has important implications for determining retirement policies. Further experiments on the differential decline in various mental tasks are planned for the coming year.

It is most desirable that older subjects living in the community be enlisted as subjects for further studies of the aging process.

GRANTS AND TRAINING BRANCH

The Grants and Training Branch (J. Franklin Yeager, Chief) is concerned with the administration of the following programs: research grants, construction grants, training grants, traineeships, and research fellowships. The processing of applications for research grants for review by the National Advisory Heart Council is carried on in close relationship to the Division of Research Grants. Applications for construction grants in the past have been handled chiefly by one person who also has processed similar applications for cancer construction grants; this arrangement has led to a more efficient administration of both construction grant programs, particularly in relation to mutual problems that have frequently arisen. In recent years the activity in this program has been restricted to liquidating commitments already made.

The research fellowships program continues to center in the Office of Research Fellowships of the Division of Research Grants and there has been a close working relationship between that office and the Grants and Training Branch. The rest of the grants and awards programs have been administered entirely within the Heart Institute through its Grants and Training Branch.

These grants and awards programs have continued to support research and training aimed at a better understanding and control of disease and public health in the cardiovascular area. Young research scientists and physicians have been given an opportunity to get additional specialized training in cardiovascular research methods (fellowships) and the care and treatment of patients (traineeships). During the several years since construction grant funds were last appropriated, commitments with regard to construction of buildings and parts of buildings for the housing of cardiovascular research have been and are being carried out; meanwhile, however, the need for cardiovascular research space has continued to grow along with an increased interest in research in the cardiovascular area.

Research Grants

Applications for research grants are recommended to the National Advisory Heart Council by Study Sections composed of scientists chosen because of competence in their respective fields. This results in careful scrutiny of the projects and consideration of the ability of the investigator, the soundness of the plan of investigation and the probable contribution of results of the research to the general field of cardiovascular disease as well as to the more circumscribed area with which the project is closely related. New and original approaches to a recognized problem are encouraged.

A total of 869 research grant applications were reviewed during the period from July 1, 1951 to December 31, 1952. The total amount requested in these applications was $10,346,478. Six hundred and thirty-five applications were approved for payment in the amount of $7,274,266 (of this amount, $189,695, covering 19 grants, was transferred to other Institutes). Because of lack of funds, 14 applications, amounting to $95,874, could not be paid.

The following tabulation indicates the distribution of research projects and the amount of support for the various categories within the cardiovascular field as of December 31, 1952. Comparison with a similar table listing the numbers of grants and the amount of support during the fiscal year 1950 shows some increase in research on blood and on various aspects of cardiovascular physiology. Aside from these, no major changes appear in the number of projects within the various categories nor in the amounts requested for carrying on the research.

Status of Heart Research Grants, by Subject Category

(Active Grants as of December 31, 1952)

Category	No. of Projects	Amount
Arteriosclerosis:		
A. Lipoproteins-cholesterol studies	21	$439,850
B. Other	18	198,550

Category	No. of Projects	Amount
Blood - including thrombosis, etc.	47	859,975
Congenital heart disease	3	35,120
Coronary heart disease	9	80,605
Electrocardiography and related areas	13	132,766
Endocarditis	3	24,629
Heart failure - including shock	25	314,158
Hypertension	49	544,679
Miscellaneous:		
Immunology	1	$ 13,197
Theoretical studies	1	6,220
Pregnancy	5	39,340
Genetics	4	48,504
Gerontology	5	67,442
Rehabilitation	1	15,282
Peripheral vascular disease	11	100,341
Pharmacology	22	190,092
Physiology:		
Cardiac	25	220,436
Renal	9	105,670
Endocrines	5	66,454
Water and electrolytes	18	203,894
Metabolic studies	21	235,372
Dynamics and mechanism of circulation	29	331,577
Muscle and nerve	5	37,300
Developmental	3	11,824
Cellular	8	106,139
Methodology, instrumentation and new drugs	17	205,970
Pulmonary Circulation	15	175,624
Rheumatic Fever:		
A. ACTH-cortisone studies	19	428,688
B. Other	11	182,364
Roentgenology	9	151,657
Special projects	3	59,500
Surgery	31	361,334
Totals	466	$5,994,553

A noteworthy accomplishment was the completion of one phase of a cooperative project on the relation of ACTH, cortisone, and the salicylates to the therapy of rheumatic fever. This study was undertaken in January 1951 by 8 teams of investigators in this country and Canada plus 6 research groups in England. A standard experimental procedure was set up so that the study would be as well controlled as possible and the various groups were in frequent communication with each other. As a result, within about a year and a half after the initiation of the study, it has been possible to recommend definite methods for treatment of rheumatic fever and, incidentally, to suggest that certain preventive measures be taken. A voluntary cooperative program of this size is unusual in medical research. Six of the eight cooperating groups in the United States were supported by grants from the National Heart Institute. These were headed by: Dr. B. F. Massell at the House of the Good Samaritan, Boston, Mass.; Dr. A. Dorfman at the LaRabida Jackson Park Sanitarium, Chicago, Ill.; Dr. E. E. Fischel, College of Physicians and Surgeons, New York City; Dr. C. McEwen, New York University-Bellevue Medical Center, New York City; Dr. J. A. Lichty and Dr. J. Githens, University of Colorado, and Dr. D. Rutstein, Harvard Medical School, Boston, Mass. Dr. Rutstein acted as the coordinator of the project.

Another cooperative study has been concerned with certain molecules, lipoproteins, found in the blood of humans and animals. These molecules, made up of fat-like (lipid) materials and protein, are of different sizes, and it has been found that certain specific ones are present in large numbers in the blood of individuals with hardening of the arteries, particularly with disease of the blood vessels (coronary vessels) that supply blood to the heart wall. A group of investigators has worked out standard techniques and has been able to secure statistically valid measurements of the concentration of molecules in human blood. In November 1952, the methods used in this investigation were discussed at a Technical Symposium, held in Chicago, Illinois. All investigators interested in these methods were invited to attend and discuss the problems inherent in research of this type and to obtain concrete information regarding the apparatus and methods used in the cooperative study. The principal investigators in this study are: Dr. J. Gofman, University of California, Berkeley; Dr. M. A. Lauffer and Dr. M. Hanig, University of Pittsburgh; Dr. I. H. Page, Cleveland Clinic, and Dr. F. J. Stare and Dr. G. V. Mann, Harvard University.

Since 1951 the National Heart Institute has been supporting research related to the National Blood Program and received an appropriation of $800,000 in 1952 for research on the fractionation, preservation, and storage of whole blood, blood plasma, and blood cells. A total of 42 grants was supported under this program during the period between July 1951 and December 1952. The appropriation for 1953 does not include funds for this purpose. Investigations carried out under these grants supported by the Heart Institute have made notable contributions to the development of methods for processing blood to be used in transfusions and in other therapy. One substance which has been isolated from blood and which is receiving widespread attention for its therapeutic properties is one of the globulins (proteins) that occur naturally in blood.

Among investigators in cardiovascular research, interest continues in clinical problems. The development of one or more types of apparatus which can act as temporary substitutes of the heart and lungs permits operations in a bloodless heart. This will assure a much greater number of successful cases of repair of congenital defects and of lesions resulting from disease. Other research on the development and use of the electrocardiograph, ballistocardiograph, vectorcardiograph and electrokymograph is aimed toward more accurate diagnosis of abnormalities in function of the heart and blood vessels.

The relation of the fat content of the blood to the mechanism of blood clotting is receiving increasing attention, not only for its importance in connection with the incidence of thrombosis but also for any connection it may have with treatment of excessive bleeding. The interrelationship between fat and protein in the blood, rather than the fat content per se appears to be important in the development of arteriosclerosis. These studies point to the significance of diet in these diseases and particularly the diet of older individuals. Important research in various aspects of this general problem is being conducted by Dr. I. L. Chaikoff and Dr. Ruth Okey at the University of California and by Dr. Ancel Keys at the University of Minnesota.

Fundamental research on the methods of functioning of heart muscle is using biochemical and biophysical techniques to explain the processes which are involved in the metabolism of muscle, in muscle contractions, and in the way in which muscle is stimulated to produce the contraction. Dr. D. E. Green of the University of Wisconsin, Dr. D. Nachmansohn of the College of Physicians and Surgeons, Drs. E. C. Andrus of Johns Hopkins University and Dr. W. F. H. Mommaerts of Duke University are among the outstanding investigators in this field who have received support from the Heart Institute. A very promising approach to the study of the minerals which are present in extremely small amounts in the blood is being supported for the first time. The work will be done by Dr. B. L. Vallee of Harvard University and will involve the use of precise biochemical and biophysical methods. The movement of salts within the body and the mechanism of their excretion by the kidneys is recognized as an important factor in various types of cardiovascular disease. A number of projects are being supported in this field, including both the biochemical and clinical methods of approach.

Construction Grants

No additional funds have been available for the continuation of this program. Of the $1,600,000 which was available for construction grants during the fiscal year 1950, all had been paid by June 30, 1952. An amount of $4,459,000 was appropriated for the fiscal year 1951 to liquidate the prior year's contract authority for construction grants and, of this amount, $3,432,940 was paid by December 31, 1952. As a result, 15 construction projects have been completed and 11 are still in progress. That these grants have an important place in the program of the Heart Institute is evidenced by the fact that 11 requests for supplemental funds and 45 requests for new construction have been received during this period. Twenty-three additional institutions have indicated that they intend to apply for construction grants.

Teaching Grants

The undergraduate cardiovascular training grant program assists medical schools in the improvement and expansion of their teaching programs in this area. These schools receive awards on the basis of a grant of $14,000 to a 4-year school and $8,000 to a 2-year school. Twenty-nine new grants, including 6 to schools of osteopathy, were made during the period from July 1, 1951 to December 31, 1952. The total number of teaching grants is 79, distributed throughout 33 States and the District of Columbia. Thus, a majority of the medical schools in the United States are participating in this program.

Clinical Traineeships

Awards are made to qualified individuals at the postdoctorate level to permit them to secure additional training in the clinical aspects of cardiovascular disease. They then return to medical practice, equipped to treat their cardiac patients according to the best methods currently available. As of December 31, 1952, 33 physicians from 13 States and the District of Columbia were currently receiving heart traineeships.

Research Fellowships

During the period between July 1, 1951 and December 31, 1952, a total of 171 fellows were working under awards from the National Heart Institute. Of these, 76 were predoctoral fellows and 95 were postdoctoral. The total amount awarded during this period was $545,694. Those awarded research fellowships have indicated they expect to devote themselves in part or entirely to research in the cardiovascular area during their professional lives; thus it is anticipated this program will help to fill the need for a greater number of well-trained research people.

TECHNICAL SERVICES BRANCH

The Technical Services Branch (R. C. Arnold, Chief) of the Institute conducts specialized activities in the field of epidemiology, biometrics research, and information. Technical assistance is also rendered to other units of the Institute where required to facilitate carrying out of specific activities or objectives.

Epidemiology Section

The Heart Disease Epidemiology Study (Thomas R. Dawber, Chief) being carried out at Framingham, Massachusetts, is concerned with the investigation and evaluation of those factors which are believed to be significant in the development or the progression of hypertensive and arteriosclerotic heart disease. A random selection was made of approximately 6,500 adults between the ages of 30 and 59--the ages in which these heart diseases most commonly develop. The plan of the study involves initial examination of the sample group with the view of doing re-examinations at 2-year intervals over a long period, during which all the data of pertinent constitutional or conditioning factors will be recorded and analyzed.

During 1952, the initial examinations were completed and the group selected for repeated follow-up examination was clearly defined. This group constituted 4,486 people, or 68.6 percent of the originally selected group. (75 percent of those actually available).

With the completion of the initial examination, attention was also given to re-examinations and continued efforts were necessary to recall those selected for follow-up studies. To date there appears to be little loss in the follow-up by refusal to continue to cooperate.

During the year, 2,991 persons went through the clinic examination. Of these, 606 were initial examinations, 2,256 were re-examinations, and 129 were special examinations of interested visitors, public health workers, etc.

From now on, attention will be devoted entirely to the re-examinations of the follow-up group to determine the development of change in cardiovascular status. An attempt will be made to observe what factor or factors correlate with the development of these changes.

Coding of the records on the randomly selected 4,486 people were completed as were those on an additional 723 persons who have volunteered for follow-up studies. This information has been put on punch cards. The report of the data so obtained will be available for publication early in 1953. Following this more detailed studies will be carried out using this data.

During the year, a study on "The Electrocardiogram in Heart Disease Detection" was completed and published. A similar study on the value of the chest X-ray or photofluorogram for screening purposes was carried out. A complete report of this study will be available in 1953.

Studies on other possible methods of early heart disease have been started and will be completed during the coming year.

Several informal discussions of the Framingham study have been participated in by staff members. There have also been consultations with several State health departments and heart associations and with numerous individuals interested in problems of chronic disease, heart disease detection, and epidemiology in this field.

Considerable effort went into a revision and improvement of the forms in use to enable us to accumulate and use additional data pertinent to the development of cardiovascular disease.

Biometrics Research Section

The Biometrics Research Section (Felix E. Moore, Chief) carries out its own program of research and at the same time provides statistical consulting services for other activities of the Institute. The Section also provides statistical information and consulting services outside the Institute to other agencies, public and private, engaged in cardiovascular disease research.

The Section has assembled data forming a historical time series on mortality from the various forms of cardiovascular disease from 1900 to the present. In the course of this work, close working liaison has been maintained with the National Office of Vital Statistics, and the Section is now working with N.O.V.S. on plans for studies of the accuracy of reporting causes of death. One result of the compilation of this time series was the publication of a semipopular publication on the statistics of cardiovascular diseases.

A major activity of the Section is the provision of statistical services for the Framingham Heart Epidemiology Study. These include the design of coding schemes and punch cards, and assistance in the revision of examination forms. Staff of the Section is now working with the Framingham staff in preparing analyses of the data, and in particular are taking responsibility for studies of the representativeness of the respondent group.

On two Nation-wide cooperative studies financed by research grants of the National Heart Institute, the Section has provided continuing statistical consultation over a considerable period of time. These are the Cooperative Study of Rheumatic Fever being carried out in eight centers in the United States and Canada, and the Cooperative Study of Lipoproteins and Atherosclerosis which is being carried out in 4 widely separated centers in the United States. In the latter study, the National Heart Institute has, at the request of the National Advisory Health Council and the cooperating centers, agreed to undertake the statistical processing of the data being accumulated by the group.

The Section has provided advice on statistical problems related to the heart disease control program to the California and New York State Health Departments. Likewise, statistical consultation has been made available to research grantees in various parts of the country.

The Institute's medical research program draws upon the section for advice on statistical design of experiments and problems of analysis, as well as for help in general mathematical problems. This activity has resulted in original research in statistical theory and the publication of 3 papers in the period covered by this report.

Finally, mention should be made of the continuing responsibility for providing information to the public on the statistics of the cardiovascular diseases. This is done by response to letters of inquiry, and by providing the Heart Information Center with data for use in articles and other forms of public release.

Heart Information Center

The Heart Information Center (Lealon E. Martin, Chief) operates as an integral function of the National Heart Institute--and at the same time as an aid to the several other activities of the Institute. Thus, the Heart Information Center seeks to provide the regular, normal services which should be expected of a Federal public and professional information and relations office--as well as projects and programs to carry out statutory objectives.

The work of the Heart Information Center has been both broad in range and intensive.

The planning, production, distribution, and utilization of publications, for professional and for public audiences, forms one of these areas of work. For professional audiences, the following are examples: Diseases of the Heart and Blood Vessels - Facts and Figures, a statistical brochure done in cooperation with the American Heart Association; assistance in the further development of the Heart Bulletin, a nationwide journal for private physicians; and Prevention of Rheumatic Fever, a brochure for physicians.

For public audiences, there was developed: A Living Pump, an illustrated leaflet on the physiology of the heart and circulation; and The National Heart Institute, a booklet telling what the Institute's program is.

Audio-visuals. Production of audio-visuals for professional groups included: development of slides and charts for use in talks by staff; and assistance in the cooperative development of a new medical teaching aid, a course in normal and abnormal heart sounds presented through tape recordings and transcriptions, for medical schools and societies' use. For public audiences: The Human Heart, a series of eight fifteen-minute dramatic radio recordings on heart disease subjects, featuring eminent cardiologists as guest speakers and famous actors playing the story roles, was developed and has been widely used; and a television presentation, over Dumont network and in cooperation with Johns Hopkins University, on the heart and circulation.

Exhibits and Other Graphics. Examples of work on exhibits, in the professional audience field are Public Health Service Aids to the Professions in Cardiovascular Education, an exhibit presented at meetings of the American Medical Association, National Medical Association, Southern Medical Association, and scheduled for a number of other large assemblies during 1953; and a new exhibit based on NHI cooperative work on a new anti-rheumatic, anti-arthritic drug. For public groups: a new series of photo stories reporting on heart research was produced as tie-ins with publication of scientific papers and to feature research progress.

Papers, speeches, articles, fact sheets and other items such as reading lists and informal bibliographies. For the professions, by way of illustration: an article, Profile of Cardiovascular Research, illustrated, prepared for NHI Director for New York Health News; and a paper on heart disease and public health for a public health association meeting. For the public, examples include articles on heart disease and industry and progress against heart disease for People's Encyclopedia and special reading lists, bibliographies, fact sheets, and background information sheets on various aspects of cardiovascular problems were prepared for both public and professional uses.

News releases and other services to the media of communication are also a main aspect of Heart Information Center activity. General releases and professional journal-science writers' releases are issued when a research accomplishment or a program activity warrants recording. The philosophy behind this is that there is an obligation to report but not to propagandize upon what the Institute work and program are. Releases are therefore based upon research discoveries, such as the contribution by Institute scientists of new knowledge about atherosclerosis which was the subject of a release keyed to a scientific paper published by Science as its lead article, and upon such things as annual reviews of the teaching and traineeships grants program. Other services to newspapers, magazine, television, radio, and other media form a continuing area of work, handled by working with writers, and others, personally, over the telephone, and by correspondence. In the course of a year, the Heart Information Center performs numerous services of this nature.

Inquiries, other than from media but both from the public and from people in the medical and health professions, occupy an important sphere. Every inquiry, whether from a person who seeks "that new drug that cures heart attacks," a man who claims he has discovered a cure for all heart disease, or a physician asking for up-to-date information on a new high blood pressure drug hexamethonium, or a state health educator asking for exhibits ideas and materials is treated with care and sincerity.

Services of other various kinds make up another category of activity and involve a variety of endeavors performed with or for non-Federal groups and for other branches of the NHI, the NIH, PHS, FSA, and National Advisory Heart Council. One illustration is assistance in arranging for various meetings and special programs, such as the annual joint staff meeting of PHS, NHI, and American Heart Association and a series of informative seminars for NHI staff in-service training. Another type of these services is that of reference research, editing, clearance, production, distribution, and utilization functions, which involve many duties. By way of illustration are these: arranging for reviews, clearance, and processing of professional and non-professional papers, speeches, articles, etc. by NHI staff or by others; development and production of NHI staff memos and orientation materials; assisting in preparation and editing of a number of scientific papers; preparing special materials for and carrying out requests of the heart council, such as data on progress of The Heart Bulletin and wide dissemination of professional information in connection with a new program of emphasis on prevention of rheumatic fever.

The Heart Information Center also serves as principal liaison with the American Heart Association with respect to information and, working collaboratively with the Association and the Heart Section, of the Division of Chronic Disease and Tuberculosis, develops projects and materials and carries on a continuing interchange of information.

Reports: During the past year, over 20 regular and special reports have been prepared by the Information Center in whole or in part. Typical of these are: annual NHI report; selected research accomplishments; semi-annual report of publications; quarterly administrative records (honors and awards) report; Information Center reports to NIH, PHS, FSA; NHI accomplishments in 1952 (for use in connection with 1954 budget); reports to heart council; advances of 1952 in heart research; summaries of research grants projects; and a report on the history and program of the NHI.

NATIONAL INSTITUTE OF DENTAL RESEARCH

H. Trendley Dean, Director

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NATIONAL INSTITUTE OF DENTAL RESEARCH

July 1, 1951 -- December 31, 1952

Introduction

In the fourth year since the National Institute of Dental Research was established by Act of Congress, the chief field of research continued to be dental caries, in recognition of the fact that it is still the most widespread disease of civilized man. Other fields of research were periodontal disease and ulcerative gingivo-stomatitis. The Institute has been functionally organized to include basic research laboratories of Oral and Biological Chemistry, Oral Bacteriology, and Functional Morphology; clinical investigations laboratories of Surgery and Prosthesis, Dental and Periodontal Diseases, and Growth and Development; an Epidemiology and Biometry Branch; and an Extramural Activities Branch. It is within this organizational framework that expansion into clinical research on oral diseases will occur.

The major portion of dental research has been done at the National Institutes of Health in Bethesda, Maryland. Some of the research work, however, was continued at field stations. These included U. S. Public Health Service Hospital at Stapleton, Staten Island, New York; and the Eastman Dental Dispensary of Rochester, New York. The Institute also continued to maintain operations at Grand Rapids, Michigan, in connection with water fluoridation studies.

LABORATORY RESEARCH

Epidemiology

F. A. Arnold, Jr., Associate Director, is in charge of research. The Grand Rapids-Muskegon study on the effect of fluoridation of water supplies for reduction of dental caries was continued. This study has been in progress since 1944 and is a cooperative study with the Division of Dental Public Health and the Michigan Health Department. Dental examinations were made in the fall of 1952 on approximately 6,000 school children in Grand Rapids and 3,000 school children of Muskegon. The results of these examinations show that there has been a reduction in dental caries rates in Grand Rapids following the fluoridation of the city water supply. The amount of reduction varies from 66.6 percent in the 6-year-old children to 18 percent in the 16-year-old children. As originally planned, the study is to run for 12 to 15 years, with dental examinations and bacteriological studies each year. This extended period is necessary to fully evaluate fluoridation as a caries control procedure. A report of the results to date are the subject of a manuscript submitted for publication in Public Health Reports.

In addition to the dental examinations of this study, research was continued in respect to bacteriological and chemical changes in the salivas of these children. During the year about 1,500 saliva samples were cultured to determine changes, if any, in the counts of acidogenic bacteria, especially lactobacilli. Also a group of about 500 salivas were analyzed to determine whether or not changes in certain chemical constituents have occurred. It is too early at present to evaluate the results of this work.

A study was started by Albert L. Russell on the epidemiology of periodontal disease. Its aim is to define the epidemiological characteristics of the periodontal diseases. At the outset there was no fully acceptable epidemiological yardstick for the measurement and comparison of periodontal disease. Such as measure, tentatively referred to as the "periodontal index" was devised upon theoretical grounds and modified as indicated by experience in its application to about 600 persons in Colorado Springs and Boulder, Colorado; about 120 uranium miners; and about 4,000 elementary and junior high school pupils in Montgomery and Prince Georges Counties, Maryland. In its present form, the index expressed the periodontal status of a tooth or of a person as a simple numerical score. In magnitude, it corresponds with clinical diagnoses, such as "normal," "mild gingivitis," "advanced marginal periodontitis," etc.; it can be analyzed by conventional technics for the appraisal of means; and when applied by highly-trained examiners to children, the results obtained were highly comparable.

With the usefulness of this tool established on a reasonable basis, it is planned to put it to use in field studies aimed at definition of such broad epidemiological foundations as differences in the character and prevalance of disease with age, sex, race, socio-economic status, and residence. Eventually studies of co-existence with other physical conditions may be carried out in the Clinical Center.

A study was started which has as its aim the development of improvements in the standardization of dental caries (DMF) examinations and reporting, in order to facilitate the utilization, for dental research purposes, of the large amount of DMF data obtainable in connection with dental health examinations of school children. A comparatively large amount of DMF data from various localities in the United States has been obtained already in connection with this study. These efforts appear to have encouraged also a number of dental directors to prepare their data on dental examinations of school children in a form suitable for publication, which would make such DMF data available to dental research workers for study and comparison of the DMF rates of various communities in the United States.

An oral health study is in progress in Montgomery and Prince Georges Counties, Maryland. The study plan contemplates the minute observation of oral health in a population of children as it becomes, progressively, less susceptible to dental caries as a consequence of fluoridation of the community water supply. Not a test of the fluoride-dental caries relationship, it will be analyzed by "horizontal" techniques, i. e., examination schedules for individual children will be matched year by year, with findings expressed as mean changes per time period per individual and compared with an intricate family of base-line expectancies established on data from the initial examination. This is an integral part of the investigation of the epidemiology of periodontal diseases being conducted by Dr. Russell. Approximately 4,400 elementary and junior high school pupils were given initial DMF examinations in January and February 1952, and will be repeated yearly so long as it continues to yield significant information.

A study was started by Eugene R. Zimmerman on the influence of climate on water ingestion and dental fluorosis. The relationship was tested in a preliminary study by a rough and indirect method of estimation. It consisted of selecting fifty-six cities in eleven states, obtaining their climatological data from the weather bureau and their fluorosis scores from surveys conducted by several investigators, and plotting the results. Inspection of these data suggests that both temperature and humidity may be factors in influencing the degree of dental fluorosis, although they do not exert equal weight at different fluoride concentrations. The purpose of this study is to determine whether or not climate can so modify a person's drinking habits and dental fluorosis response that seasonal allowances must be made in the fluoride level of a water supply.

Chemistry

For a period of about 2 years, a diet containing 80 percent of dry cereal foods (white bread, rye bread, yellow corn grits, and oatmeal), 18 percent cerelose, and 2 percent common salt, has consistently produced a particularly significant type of surface and occlusal caries in white rats. An apparently justifiable hypothesis, in explanation, is that the production of these lesions might be influenced by the protein deficiencies in this diet or be factors created by the heat processing of the foods. This work, being carried on by Frank J. McClure, seems to indicate more and more that a special form of caries is being developed by these protein and heat processed diets. James E. Folk, a Research Fellow of the American Dental Association, is making preliminary chemical studies to fractionate casein, a pure protein, into certain amino acid compounds with the objective of obtaining information on the chemical changes which result during heat treatment.

Analyses were made by McClure and P. O. Pedersen to determine the fluorine content of teeth obtained from West Greenland and Alaska skulls, and from living Greenland natives. The purpose of these analyses was to evaluate the results as a possible explanation of the low incidence of dental caries among native Eskimo people. The data obtained indicated that there is a significant source of fluorine exposure (food or water) in the Eskimo dietary. It seems most likely that the consumption of fluoride-containing seafoods contributes to the relatively higher fluoride content of the Eskimo teeth, in comparison with similar figures for dentin and enamel with no such exposure to fluorine.

A study was started by McClure and Paul Honda on the effects of iodoacetate administered perorally, by subcutaneous injection and in the diet, on induced rat caries. The pronounced preventive effects of iodoacetate on induced caries in rats has never been explained. There was an attempt also to determine the iodine content of the teeth as related to the iodoacetate therapy. Any information as to the mechanism of the iodoacetate effect would throw light on the etiology of dental caries. Additional experiments will be continued.

A study is in progress on the metabolism of fluoride under adverse dietary regimens. The data from these experiments should furnish evidence for evaluating the unsubstantiated claims that undernourished groups of children and adults may be more susceptible to an adverse effect of fluoride waters than adequately nourished groups.

Experiments were made on the effect of stannus fluoride in the drinking water on induced rat caries in comparison with sodium fluoride. There was no apparent difference in the anti-caries effects of these two fluorides.

A study was started by Robert C. Likins and Isadore Zipkin on the effects of various concentrations of sodium fluoride in the drinking water of growing pigs. This study should reveal additional information which is desirable regarding the physiological effects of fluorine, particularly an investigation of the soft tissues. Samples of body tissues have been taken and are in the process of chemical analysis and histological examination.

A study was started on urinary fluorine excretion by populations using domestic waters fluoridated to a concentration of one part per million of flouride (F), using the urinary excretion as a criteria of similarity of effects of different fluoride waters. Data from two areas using different fluorides will be compared with natural fluoride water exposures.

A study is in progress by Likins to determine the urinary fluorine excretion following defluoridation of a water supply of a community which had been drinking, for many years, water containing naturally about eight parts per million of fluoride (F). Results will give some idea of the magnitude of fluorine storage by various age groups and the extent to which the body may eliminate its fluorine deposits at different periods in the life span.

A study is in progress by Likins and Zipkin which has as its aim the determination of the rate of absorption of various fluorine compounds from the gastrointestinal tract, to learn if various fluorine compounds available for fluoridation purposes are absorbed at different rates of speed.

A study of various chemicals, which might behave similarly to citrate solutions in decalcifying rat molars when given in the drinking fluid, is in progress by McClure and Zipkin. Of the many compounds already investigated, a few commercial chemicals, sold under various trade names, were found to be active agents in producing similar decalcification. A study is also in progress on the relation of decalcifying agents to dental caries.

In connection with further studies on the citrate content of saliva, and its relationship to dental caries, Zipkin and Robert M. Stephan collected samples of saliva directly from the parotid glands for analysis. Preliminary results indicate that parotid saliva may be comparatively rich in citrate.

A study was started by Zipkin and Arnold on the sodium and potassium content of saliva in relation to dental caries. It has been shown that lactobacilli require an optimal Na/K ratio for growth. If the thesis that lactobacillus counts are related to DMF be accepted, perhaps some correlation may exist between DMF and the sodium-potassium ratio.

Zipkin and Karl Piez started a study of the changes in the protein of rats' teeth on protein deficient diets in an effort to help explain the caries mechanism and answer the question whether carious teeth have an altered protein composition.

Work is in progress by Likins and Zipkin on a study of the effect of fluorine deposition in the rat on the rate of calcium deposition, to determine whether individuals consuming fluoride have any abnormal rate of calcification.

The study on the reactions of fluoride with hydroxyapatite, enamel, and dentin was continued by H. C. McCann. In the case of the hydroxyapatite, it was found that fluorapatite is formed at all its Ca/P ratios at a fluoride concentration of a few parts per million as occurs in natural waters. At higher fluoride concentrations,up to 0.2 percent, calcium fluoride or fluorapatite is formed depending on the Ca/P ratio of the apatite, while at still higher fluoride concentrations, calcium fluoride is formed in large amounts regardless of the Ca/P ratio. Publication of the findings in this experiment is now in process.

Experiments were made by McCann on a spectrophotometric procedure for the determination of fluoride. The color developed by the proper ratio of sodium alizarin sulfonate and thorium nitrate is stabilized by means of gum arabic. It appears to possess a stable, reproducible, color relationship to the fluoride. The procedure still needs, however, to be tested to determine recoveries of fluoride from sodium fluoride alone, and when added to urine and tooth samples.

Oral Bacteriology

Research work was continued by Morrison Rogosa on lactobacilli of the human oral cavity. Almost one dozen species or sub-species of lactobacilli have been found to occur in the human mouth. Two of these are probably hitherto undescribed new species. A working "Key" has been devised to facilitate separation and identification of oral lactobacilli. The nutritional patterns and biochemical activities of some 700 strains of oral lactobacilli have been thoroughly worked out for the first time. With this basic information available it should finally be possible to assess with precision the role of members of the genus Lactobacillus in the development of dental caries.

A study is also in progress by Rogosa to determine the changes in the bacterial oral flora of the hamster which occur with the development of caries. Preliminary indications are that the hamster shortly after weaning has a large number of lactobacilli and few streptococci present in the oral cavity. As the animal grows older this picture is reversed. There are great qualitative differences in the types of lactobacilli found in the mouths of humans and hamsters. For example, almost one-fourth of the hamster lactobacillus strains appear to be members of a new species which has been found only rarely in human saliva. On the other hand, L. casei, which is the predominating homofermentative organism in humans, has not yet been found in over 450 hamster isolates.

In connection with an investigation of the etiology of ulcerative gingivostomatitis, by Edward G. Hampp, an American Dental Association Fellow on duty at this Institute, work is in progress on methods for separation of the smooth and rough types of the spirochetal organisms so that only smooth types of spirochetes may be employed in serologic studies. Experiments are also in progress to gain further knowledge of the relationship of the spirochetal granules to the life cycle of the organism. Borrelia buccale was isolated in pure culture for the first time. Studies are in progress on its growth requirements and on the development of a routine technic for isolation and pure cultivation of this organism.

In studies on the fusiform bacilli, by Robert R. Omata, another American Dental Association Fellow, paper chromatography was applied in the separation and identification of the lower volatile fatty acids, which are known to be metabolic products during the growth of some of these bacteria. Some success has been achieved in the use of this method in identifying bacterial strains.

In continuation of studies on the effect of antibiotic agents on caries in rats by Robert J. Fitzgerald and Robert M. Stephan, penicillin and bacitracin were found to be very effective, even in relatively low concentrations, in controlling either smooth surface or occlusal caries in rats. Results of bacteriological studies have failed to indicate any definite positive or negative correlation between lactobacilli, streptococci, yeasts or coliform organisms and the caries picture in the experimental animals.

Various enzymatic activities of the oral microflora have also been studied by Fitzgerald. One of the most interesting of these is the enzyme acid phosphatase possessed by a number of oral bacteria and yeasts and which is remarkably sensitive to the fluoride ion. There is the possibility that such an enzyme might bear a relationship to the dental caries process.

In conjunction with workers conducting various nutritional and inhibitory experiments on rat caries, Fitzgerald and Jordan are studying the rat oral microflora in an attempt to discover how the types of oral bacteria may be related to diet and caries development. In this work it has been found necessary to conduct fundamental studies on the taxonomy and classification of the rat oral bacteria as most of these organisms differ from those found in the human oral environment. For example, several hundred strains of lactobacilli have been studied extensively and found to be unlike the lactobacilli described by Rogosa from humans and hamsters. In addition to their possible significance in the rat oral environment some of these strains exhibit unusual metabolite requirements which on further study may add to our knowledge of bacterial and animal nutrition.

Although the parasitic oral flora, nutrition, physical properties of the diet, and heredity and sex have all been found to exert an influence on dental caries, nevertheless unexplained variation is still observed in the development of caries in individuals. It is particularly evident in animal experiments in which the common variables of diet, genetic strain, litter, and sex are controlled. This indicates that the initiation of caries is dependent upon the combined interaction of several different factors. In laboratory studies on the etiology of dental caries, work is in progress by Stephan on a multifactorial experiment with rats, testing agents which increase caries against agents which decrease caries, each at three quantitative levels, and both with or without the modifying effect of coarse particles in the diet. Experiments for testing the effects of different nutritional supplements against the effect of variations in the physical properties of the diet on experimental caries have shown that both nutrition supplements and physical changes in the diet can greatly reduce the development of caries in rats.

Evaluation of dental caries in about 8,000 rats from experiments conducted in the nutrition section of NIAMD is in progress and about half completed. All types and degrees of dental caries have been found among these animals. Correlation with diet should be very interesting.

In connection with studies of caries in rats, observations have also been made as to various degrees of periodontal involvement. About 7,000 rats have thus been examined. Analysis of these data should suggest specially designed experiments for periodontal studies.

Functional Morphology

Studies were made by David B. Scott and John T. Albright of carious enamel and dentin, as seen under the electron microscope in thin sections. Of principal interest to date has been the observation of the location of microorganisms found in both enamel and dentin. Definite conclusions have not been reached, especially with respect to the orientation of microorganisms in enamel, but the sequence of events occurring in invasion of the dentin appears to be first filling of the dentinal (Tomes') fibers with bacteria, followed by complete filling of the tubules, rupture of the tubules, and finally invasion of the matrix. There are also indications that in both enamel and dentin some demineralization may precede bacterial infiltration.

In experiments designed to develop new procedures and improving technics for handling and sectioning of dental tissues for electron microscopy, special emphasis was placed on fixation and demineralization. Work was done also on the handling of undemineralized carious dentin and enamel.

In continuation of a study on the effect of sodium fluoride on human enamel, experiments were made with enamel slabs treated thirty days with two percent sodium fluoride. Selective grinding has demonstrated that the layer of calcium fluoride, as identified by diffraction, is not over 25 microns thick. However, chemical analysis has indicated that considerable fluorine is present in the enamel beneath the calcium fluoride layer. Work is in progress with the aim of determining whether the fluorine in the subsurface enamel is present as calcium fluoride or fluorapatite.

Previous replica studies of tooth surfaces have indicated that estimations of individual age can be made through examination of remaining structural detail. It was noted that such strong indications of age changes are given by the perikymata that it may be possible to estimate age by their study alone at low magnification. The work in progress is directed at development of a method of age determination involving only examination of tooth surfaces under a low power microscope, and comparison of the perikymata pattern with standard charts, showing the pattern at various age levels. Charting of perikymata patterns visible on surfaces of teeth from individuals of known age, preliminary to preparation of standard charts, is in progress.

Work was continued by Arden Howell on studies of the relationship of pathogenic fungi to diseases of the oral cavity. In order to study the incidence and identity of species of Actinomyces occurring in the oral cavity, about 14 strains of fungi isolated from human or animal sources, were studied as to morphology, type and form of colonies on various media, type of growth in liquid media, ability to ferment various carbohydrates, and ability to grow under aerobic or anaerobic conditions.

A study is also in progress by Howell on the effect of antibiotics and/or chemotherapeutic agents on pathogenic fungi. Most of the known antibiotics have been found to be ineffective against the pathogenic fungi with the exception of Actinomyces, which has been shown to be susceptible to the action of penicillin, streptomycin, chloramphenical, and aureomycin. Some experiments were made to determine the effect of a few other antibiotics and chemicals on one or more pathogenic fungi, such as candida albicans, Cryptococcus neoformans and species of Actinomyces. The results have been encouraging.

Since standardized procedures for producing an LD_{50} for most of the pathogenic fungi in experimental animals are not available, experiments are in progress by Howell with the aim of developing a suitable procedure for determining an LD_{50} for Cryptococcus neoformans, and Candida albicans, using mice as experimental animals.

A study was started by Herbert J. Bartelstone on the secretion of radioactive iodine by salivary glands of humans and cats. In work with six cats and two humans, using I^{131} the concentration of the radioactive iodine in the saliva followed the blood curves in four cats, in the other two cats, there was a significant peak 6 and 12 hours after administration of the dose, at a time when the blood level was falling. In both human cases, the concentration of the radioactive iodine in the saliva was higher than in the blood throughout the 24 hours during which hourly samples were collected.

Work was also done by Bartelstone on the development of a radioacutographic technic for tooth sections analogous to superimposed radioautographic technic for soft tissues reported in the literature. Emulsions on the market have been screened and one has been selected for experimental trials. The developed technic was applied to a study of in vitro penetration of I^{131} into human teeth. About 150 sections with superimposed radioautographs have been examined. It was observed that there is a diffuse penetration of enamel with increase in uptake in areas of lamellae (cracks). There may be a correlation between lamellae with protein material in them and the presence of increased uptake of I^{131}. Pre-carious and carious enamel, as well as poorly calcified enamel show increased uptake. Penetration along paths of changed dentin is seen early especially near a carious area. Enamel uptake is greater in the outer one-third and decreased toward the dentino-enamel junction in normal enamel.

A study was started which aims to determine whether the albumin molecule can be shown to penetrate the intact enamel of cat teeth. A commercial preparation of I^{131} tagged human serum albumin was used in these experiments. After application to the enamel surface, evidence of radioactivity within the tooth was found in about 25 percent of the cases. Further experiments, however, will be required to prove that the I^{131} has not dissociated from the albumin at a faster rate than anticipated.

A study is in progress by William B. Savchuck on the effect of strontium and fluoride on bone repair. About 60 male adult rats, the left humerous of each of which was fractured, were distributed into four groups on the basis of grade of fracture as determined radiographically. Each group received, beginning with the sixth week of the postfracture period, measured quantities of drinking water of one of the following compositions: 1.) 0.002N fluoride (38 ppm. F.), 2.) 0.002N strontium, 3.) 0.002N fluoride and strontium on alternate days, 4.) tap water. The animals were sacrificed 12 weeks after fracture. The normal and fractured humeri were then tested for breaking strength. Under these conditions, bone repair appeared to proceed quite independently of the strontium or fluoride supplements. Other phases of this study are also in progress.

DENTAL RESEARCH GRANTS

In the year 1952, forty-two research projects were supported by dental research grants. These researches continued to be carried out mostly at universities and colleges; and the remainder, in hospital laboratories. These researches included fourteen projects which may be considered as relating to some phase of dental caries and aiming to aid in its prevention.

Other subjects studied included the etiology of periodontoclasia; relation of vitamin C to periodontal disease; endocrinological factors in periodontal disease; production of periodontosis in the spider monkey; blood supply and its control in periodontal membrane; inducing repair in periodontal membrane; establishment of a quantitative method of indexing gingival disease; histopathology of gingivae in systemic diseases; transplantability of salivary gland tumors; malocclusion with special reference to heredity; relationship between muscle forces and dental facial anomalies; bone and tooth development as influenced by vitamin B deficiency; relation of developmental factors, other than nutritional, to tooth form in the rat; prenatal influence on development of teeth and supporting structures; operating characteristics and efficiency of dental hand pieces; effect of abnormal muscular tensions upon the sites of growth of the cranium and face; effects of metabolic factors upon tissue changes incident to tooth movement; masticatory function of children; effect of ACTH and cortisone on pulp reactions and dentin disposition in fully erupted teeth; development of the mandibular arch and teeth in amblystoma punctatum; growth of tooth germs in vitro; calcification of teeth and bones; X-ray diffraction study of the structure of normal and treated enamel of teeth; growth changes in head, face and teeth during changing dentition; solubility of oral calculus in saliva as influenced by carbon dioxide; cellular respiration in dental tissues; and the microstructure of dental amalgam.

DENTAL RESEARCH TRAINING

The purpose of the dental research training program is to aid and encourage qualified dentists and other college graduates to enter the field of dental research by providing adequate training in the application of basic sciences to dental research. Since dental research is a comparatively new field, it has been found difficult to obtain qualified personnel to conduct dental research. Prior to the recently awakened interest in dental research, following closely the demonstration of the fluoride-dental caries relationship and the possibility of reducing dental caries through proper adjustment of the fluoride concentration of drinking waters, dental colleges gave little attention to training in research. Most dental graduates were interested only in practical operative dentistry and lacked sufficient training in dental research. Until the dental colleges are enabled to adequately fill this need, as many medical schools have done in the medical field, such a supplementary training program will be highly desirable.

During this fiscal year, there were sixteen active fellows in the field of dentistry. Their research subjects included the metabolism of pyruvate; chemical composition of human saliva; drinking response to injection of hypertonic salts; electromyographic analysis of muscles of mastication in normal and abnormal conditions in man; mechanism of carbonate effect on apatite solubility; physiological effect of fluorine upon enzyme systems; etiology of periodontosis; effects of systemic diseases upon the oral cavity and vice versa; serologic reactions of lactobacilli; possible role of inheritance in the development of dental caries in the Syrian hamster; in VIVO study of the permeability of intact and carious hamster enamel to isotope labeled compounds; salivary protein putrefaction; adrenal cortical function after hypophysectomy; cadmium intoxication in rats; and growth of dental anlagen when subjected to heterologous transplantation under various types of controlled conditions.

NATIONAL MICROBIOLOGICAL INSTITUTE

Victor H. Haas, Director

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NATIONAL MICROBIOLOGICAL INSTITUTE

July 1, 1951 - December 31, 1952

INTRODUCTION

The National Microbiological Institute, established as an Institute in 1948, is responsible for conducting, coordinating, and stimulating fundamental research in the broad field of microbiology, and for the operation of a national program of biologics control. To carry out its responsibilities, the Institute is organized into Laboratories of Infectious Diseases, Tropical Diseases, Biologics Control, Clinical Investigation, the Rocky Mountain Laboratory, and an Extramural Programs Branch.

The work of this Institute has undergone shifts in emphasis and in approach to meet new problems, new knowledge, and new public health needs. In past decades, microorganisms were significant in terms of death rate and disabling illness; today their primary significance derives from their importance in terms of aggregate illness and economic loss. Virus and rickettsial diseases now demand the same emphasis that bacterial diseases required in past years. Bacterial diseases, on the other hand, necessitate a new approach, in the light of current national need, along such lines as developing new and better techniques and more effective application of known techniques to meet hitherto unknown implications that might develop in terms of possible defenses against potential agents of biological warfare.

These are the factors that make microbiological research dynamic in nature. Much still remains to be learned in many branches of this research area. Objectives must be pursued vigorously and redefined in light of new knowledge, not only to maintain existing public health gains but to fill the gaps in neglected and lagging areas of study.

LABORATORY RESEARCH

Laboratory of Infectious Diseases

Karl Habel is chief of the Laboratory of Infectious Diseases. The general objectives of the Laboratory continue to be the study of infectious diseases -- their causative agents, their occurrence in nature, the disease they produce, how it is produced, its prevention and cure. In each of these categories a fundamental investigation of factors involved and how they operate as well as an application of those basic facts to the disease problem in nature are possible. In general, the diseases and agents studied are those more strictly classified as infections in man.

During the past year the laboratory organized a new unit on Bacterial Metabolism. This unit has broad interests in the metabolic aspects of mammalian as well as bacterial cells and is expected to cooperate in fundamental studies of viral as well as bacterial and fungal agents.

Cooperative work between the Laboratory of Infectious Diseases and the Institute's newly established Laboratory of Clinical Investigation has already been productive, as evidenced by the studies of Coxsackie viruses in poliomyelitis patients in Children's Hospital, Washington, during 1952.

Further contributions of the Laboratory of Infectious Diseases to the over-all program of the Microbiological Institute are indicated in the reports on the WHO Influenza Study Program in the northern part of the Western Hemisphere and the Sectional Research Program of the Grants Branch, both of which receive their scientific direction from this laboratory.

Section on Basic Studies

Physical Microbiology Unit. The principal objectives of this unit, directed by Dr. Herman DuBuy, have been to try to show (1) that mitochondria of animal origin possess extranuclear, hereditary properties and are the carriers -- possibly the sole carriers -- of the carbohydrate, fat, and protein metabolizing enzyme systems in the cell; (2) that many viruses which might be considered as mitochondrial derivations multiply on the mitochondria or mitochondrial modifications in vivo or in vitro; (3) that once the requirements for virus multiplication are established, the proper antimetabolites can be investigated for their antiviral properties.

Three major accomplishments have been reported by the unit in the past year. They are (1) in vitro staining of mitochondria with Janus green B; (2) demonstration of the carbohydrate metabolizing enzymes in the mitochondria; (3) localization of the early growth of enteric viruses to the mitochondria in infected cells. These new findings supply additional evidence pointing to the major significance of mitochondria in cell metabolism and their possible importance in the multiplication of certain viruses.

Basic Immunology Unit. The over-all objective of the unit is to contribute to the understanding of the phenomena of immunity and hypersensitivity. To this end, Dr. Robert Hanan and his assistants have been investigating the effect of ultraviolet irradiation on the reactivity of antibody and also the mechanism of the suppressive effect of cortisone on antibody production in rabbits.

The irradiation study, of interest because of the changes this measure induces in antibody reactivity, involves the use of almost all immunological techniques and various physio-chemical and chemical techniques. Ultracentrifical studies of irradiated antibody have provided evidence that the increased continuing ratio of irradiated antibody in vitro, previously noted by the investigators, is due to an increased asymmetry of the antibody molecule.

In collaboration with Dr. John Overman, also of the Laboratory of Infectious Diseases, Dr. Hanan and his staff have compared the suppressive effect of cortisone on antibody production in rabbits to three different antigens: serum albumin, mumps vaccine, and sheep red cells. Antibody to serum albumin was suppressed in all the animals tested; antibody to mumps was suppressed in some but unaffected in others; and antibody to red cells was not suppressed in any of the animals tested. The results suggest that the suppressive effect of cortisone is related to the particle size or physical state of the antigen.

Section on Experimental Therapeutics

Emergence of Resistance to Antibiotics. These studies, under the direction of Dr. Harry Eagle, are continuing, with chloramphenicol and fecalis as a model system, to determine whether the emergence of resistance to antibiotics regularly involves the selective outgrowth of spontaneous mutants present in the original population. There is, however, the possibility that in some cases resistance may develop as an adaptive response to the presence of the antibiotic. In effect, this would imply the inheritance of acquired characters and would constitute a phenomenon of broad biologic significance.

Mode of Action of Penicillin. In one approach to this problem, Dr. Eagle and Dr. Arthur Saz are studying the degree to which radioactive penicillin is bound by normal and by penicillin-resistant organisms, as well as the chemical fraction of the cell with which the penicillin is associated. They have found that penicillin is strikingly concentrated by bacteria and, surprisingly, that normal and penicillin-resistant cells do not differ in this respect. Approximately half the intracellular penicillin is attached to protein.

Growth Requirements of Mammalian Cells in Tissue Culture. This project, only recently initiated, represents an attempt to define the specific growth requirements of different cell lines in tissue culture. Dr. Eagle and his colleagues have been successful in determining the exact growth requirements of a saprophytic organism; the techniques used in these studies should be directly applicable to the study of the mammalian cell.

Growth Requirements of Treponemata. A chemically defined medium has been developed which supports the growth of a saprophytic spirochete. Its nitrogen requirements have been defined in detail and include 13 amino acids, a pyridine, and ammonium salt. Studies are now in progress to define which of the vitamins and accessory growth factors are similarly essential for growth.

Mode of Action of Aureomycin. After an extensive study of the effects of antibiotics on a wide variety of enzyme systems, it has finally been found that aureomycin has a striking inhibitory effect on an organic nitro-reductase in cell-free extracts of E. coli and prevents, for example, the reduction of p-nitrobenzoic acid to PABA. This is the first bacterial enzyme found to be inhibited in cell-free extracts of any antibiotic, and constitutes a promising approach to the mode of action of aureomycin.

Section on Virus and Rickettsial Diseases

Respiratory Viruses. The objectives of this unit, headed by Dr. R. J. Huebner, continue to be the evaluation of minor respiratory illnesses as they occur in natural population groups. This entails the study of clinical disease in the mass as well as in the individual, its distribution and spread in the population, and the search for etiological agents along with the development of new techniques for their demonstration.

Epidemiological Studies of Coxsackie Viruses. In the past several years the epidemiological approach has been concentrated chiefly on the Coxsackie viruses, which have been shown to be among the most prevalent of human virus agents in nature and the cause of a large amount of mild clinical illness in man. After the original discovery of these viruses and of the techniques for their demonstration, their widespread presence in humans caused them to be implicated as the etiological agent for a number of clinical illnesses. Dr. Huebner and his associates were the first to collect sound scientific evidence through combined epidemiological-laboratory methods that certain Group A Coxsackie viruses are probably the cause of herpangina, a prevalent, mild febrile disease of children.

Following the leads of others which showed a possible relationship between Coxsackie Group B viruses and epidemic pleurodynia, the section studied an outbreak of this disease in northern Texas. In 16 of 22 patients, a type of Group B virus was isolated under clinical and epidemiological situations quite suggestive of an etiological relationship. Although an epidemiological survey of 600 persons in this area is still being evaluated, there is evidence that the Group B viruses are not nearly as widespread in their distribution in humans but are perhaps more intimately associated with illness than are the Group A types of virus.

During the summer of 1952 an attempt was made to collect evidence of any possible association -- suggested by several workers in this field -- between Coxsackie virus infection and the epidemic occurrence of poliomyelitis. Outbreaks of polio, varying in severity, in Maryland, Ohio, Missouri, and Oklahoma were investigated for evidence of Coxsackie virus infection, without very much evidence being found.

Laboratory Studies of Coxsackie Viruses. A rapid method for demonstrating Coxsackie viruses in human specimens has been developed by Dr. Huebner's unit, using the originally inoculated suckling mice as the source of antigen for a type-specific complement fixation test with type-specific mouse sera.

Group B viruses have been shown to cause infection, without symptoms or death in adult mice, to high titers with the subsequent development of specific complement fixing antibodies. This appears to be a more efficient and practical method than suckling-mouse inoculation for the original demonstration of these agents.

Clinical and physical studies of Coxsackie viruses have resulted in purification and concentration to the point where molecular arrangement in electron micrographs strongly suggests crystal formation with these animal viruses. This has never before been demonstrated.

Projected Studies on the Common Cold. Three approaches to this problem are planned.

Clinical and epidemiological definition of the entity or entities classified under the term, "common cold." This would entail intensive and long-term surveillance of a small population group (approximately 75 families) for characterization of respiratory illnesses and collection of materials for etiological study in the laboratory.

Etiological studies. These would employ various technical approaches with major emphasis on tissue culture methods which are now being developed using human embryo as well as animal tissues and evaluating them with known viruses (Coxsackie, influenza, and herpes).

Demonstration of pathogenic capacities of possible new agents. This study will probably involve use of human volunteers. How these experiments would be set up has not been established, but much has been learned from the difficulties encountered by others.

Poliomyelitis Studies

Relationship of Types of Poliomyelitis Virus to Its Epidemic Manifestations. Specimens were collected from 20 areas of the United States during the polio epidemic year of 1952. These are being processed to determine the types of virus involved and the characteristics of these viruses to see if any demonstrable differences in the organism can explain the varying severity of the local outbreaks of this disease.

Physiological Factors Influencing Paralysis in Poliomyelitis. Basic studies by Dr. Karl Habel and his associates on the mode of infection and the pathogenesis of the clinical disease are aimed at determining factors which decide the occurrence or absence of paralysis in human poliomyelitis. The ultimate objective of this aspect of the program is to find methods of modifying or preventing clinical paralysis in human disease. Immunization, especially with pertussis vaccine, preceding the onset of polio has been found to increase the severity of the paralysis and to localize it in the limb where the vaccine was inoculated. This has been duplicated experimentally, and evidence suggests that the mechanism of action may be through the formation of histamine. Another approach to this same problem which is continuing involves a study of the changes occurring in the central nervous tissue early in the stage of recovery from paralytic disease. There is some evidence that antiviral substances, possibly differing from antibodies, may be produced by damaged or recovering cells. The localization and nature of these substances are being studied. The importance and influence of antibody in the blood and spinal fluid during the early phase of polio infection is also under investigation. Work of others has suggested that the rapidity of antibody production may determine the subsequent occurrence of paralysis.

Infectious and Serum Hepatitis. A continuous effort has been made by Dr. Lawrence Eilham and Dr. John R. Overman to grow the viruses of serum and of infectious hepatitis in the laboratory. Most attention has been given to tissue culture. Among tissues used have been human uterine and placental tissue and whole embryo tissues of mice and hamsters. Embryonated eggs have also been tried. After seven or eight blind passages in these various media, the final preparations, in some instances, have been given to human volunteers. All starting materials and final preparations have been inoculated into suckling mice and hamsters by various routes including intracerebral, intraperitoneal, and by stomach tube. Hamsters and monkeys have also been given direct intrahepatic inoculations. Although none of these experiments has succeeded, it is felt that the medical importance of hepatitis is so great as to justify continuing the efforts to find a solution to this problem.

Mumps Virus in Relation to Hepatitis. Research on mumps virus was begun in the hope that growth of this virus by new laboratory methods might give a new approach which could be applied to the hepatitis problem. Dr. Kilham and Dr. Overman have been able to demonstrate that mumps virus may be adapted to growth in suckling mice by 20 passages in mouse embryo tissue culture. It has also been demonstrated that mumps virus will cause a fatal encephalitis in suckling hamsters and that hamster passage virus, on intracerebral passage in suckling mice, leads to a fatal disease of these latter animals.

Relation of Viruses to Tumors and Cancer. A new virus (K-virus) which the investigators believe has not been demonstrated before has been isolated from C3H mice and shown to have the unique properties of being highly fatal for suckling mice by almost any route of inoculation but leading to no apparent illness in adult mice. Inoculation of older suckling or of C3H mice of a strain free of the Bittner milk agent leads to latent infections which may be followed by virus isolations for six weeks or more. There is evidence that gestation and lactation lead to an increased multiplication of latent virus. These studies are being pursued in an effort to find out more about latent virus infections, their relation to circulating antibodies and to the age and physiologic condition of the animal.

Studies on Fibromas of Squirrels and Rabbits. In cooperation with the Patuxent Wild Life Refuge, Dr. Kilham and Dr. Overman are conducting studies of the distribution of the Shope fibroma in cottontail rabbits, its occurrence in different years, and the means by which this disease is transmitted. Aside from the fact that these studies might have definite value in wildlife management, investigation of the Shope fibroma ties in with the virus cancer problem, inasmuch as the fibroma virus does lead to tissue proliferation.

Section on Bacterial and Mycotic Diseases

Brucellosis Studies. This project, headed by Dr. N. B. McCullough, is a comprehensive investigation designed to increase understanding of the epidemiology, pathogenesis, diagnosis, clinical aspects, and treatment and prevention of brucellosis in man. Basic studies of the organisms are an essential part of the program.

During the past year the efforts of this laboratory in the field of diagnosis of human brucellosis have been, in part, responsible for the formulation of diagnostic criteria for human brucellosis by the National Research Council Committee on the Public Health Aspects of Brucellosis. Studies of laboratory methods, made in conjunction with various WHO Brucella Centers, have led to the recommendation by the WHO-FAO Expert Committee on Brucellosis of various procedures as accepted laboratory techniques in the diagnosis of brucellosis.

During the past year stable antibiotic-resistant and dependent strains of Brucella have been developed and are being employed in nutritive, pathogenicity, immunological, and enzymatic studies.

Mycology Unit. Isolations of H. capsulatum, causative agent of histoplasmosis, from animals now total 247. Host species not previously reported are the striped skunk, fox, and woodchuck. Dr. C. W. Emmons and his staff have isolated H. capsulatum from 31 specimens of soil collected in the past year from farms in Virginia and Maryland. These studies of animal hosts and saprophytic sources of pathogenic fungi have yielded information pertinent to epidemiological problems presented by the mycoses.

A careful study of 50 cats and dogs collected in Virginia provided valuable information about the occurrence and pathology of inapparent histoplasmosis in these species. Histoplasmosis was proved by culture in 44 percent of these animals, and the importance of cultures from peribronchial lymph nodes was demonstrated.

A completely synthetic medium giving growth superior to those previously reported has been prepared, and progress has been made in its further improvement and simplification.

Rheumatic Fever and Streptococcal Diseases. This unit, headed by Dr. Roger M. Cole, has as its purpose the study of diseases caused by streptococci, and the sequelae of such diseases, including rheumatic fever and acute glomerulonephritis.

Work during the past year has been chiefly on the agglutination of streptococci. Unpublished results indicate that agglutination of autoclaved streptococci is group-specific and is probably due to the group-specific C polysaccharide; agglutination of living streptococci by the same sera (prepared from autoclaved vaccines) was usually but not invariably type-specific.

Tuberculosis Studies. Headed by Dr. B. J. Olson, this unit is concerned with a combined laboratory and field study of tuberculosis and pulmonary calcification. In connection with vaccine investigations, techniques have been developed for the reliable determination of numbers of organisms in BCG vaccines. Studies have continued, in collaboration with Parke-Davis and Co., on an ultraviolet irradiated vaccine for human use. Future work on vaccines includes plans for study of chemical fractions of virulent organisms for antigenicity and other properties.

Epidemiological investigations through a long-term observation of a human population in Virginia and Alabama continue in an effort to evaluate the cause and mechanism of production of pulmonary calcification. Evidence to date would indicate that only a small fraction -- perhaps 10 percent of the pulmonary calcification in one area -- can be explained by the occurrence of inapparent histoplasmosis infection.

Diarrheal Diseases. At the New Orleans field station, special emphasis is being placed on a quantitative approach to the study on the occurrence of the type strains of E. coli which have been shown to have an intimate association with epidemic infantile gastro-enteritis. It has been shown by other investigators that cubicles may become widely contaminated within 18 hours, and that these strains may remain viable in dust for at least 27 days.

Since it has been shown that carriers of organisms of the Salmonella groups may be detected in unexpected numbers through the examination of sewage effluent first from main sewers, then from tributary sewers, and eventually from inspection chambers of drains of individual homes, it is important to investigate the feasibility of use of related methods in small towns and rural areas, not only for isolation of Salmonella but also for Shigella. Studies at the Thomasville, Georgia, field station in cooperation with CDC will continue, with development of evaluation methods (combined laboratory and epidemiology) of experimental factors and their control.

Although strains of the genus Pseudomenas are not recognized as common pathogens, they are assuming more importance in the role of "opportunists" and causative agents in true infections. Their possible significance as producers of diarrhea has not been thoroughly investigated. In bringing taxonomic approaches to the basic problem within sight of completion, a study at the National Institutes of Health of certain other characteristics of these various groups of potential pathogens may now be undertaken with the hope of learning more about the factors which contribute to their pathogenicity and virulence.

Consultation service in planning and operating a diarrheal evaluation and control program in Fresno County, California, was continued in the past year, in collaboration with both county and State health departments. This program is being expanded by the State health department.

Bacterial Metabolism. This unit was activated in September 1952, and its program is now being formulated. The unit is designed for basic research studies of the fundamental metabolic pathways of pathogenic microorganisms. In the Laboratory of Infectious Diseases, there are a number of units working with various pathogens with whom this unit will cooperate. The approach planned is to study the various enzyme systems operating in these pathogens using chemical, physical, and metabolic techniques on whole organisms or cell extracts. The ultimate objectives are the chemical and metabolic explanations of such things as virulence, specificity, pathogenicity, with of course the corollary that some specific point of attack in chemotherapy will be forthcoming.

Section on Epidemiology

Influenza Study. The chief objectives of this study on influenza and influenza-like illnesses, in charge of Dr. Joseph A. Bell, are (1) to provide an opportunity to observe the clinical nature and mode of occurrence of acute febrile respiratory illness in family households of various communities; (2) to obtain throat washings, cultures, and acute and convalescent serum specimens in an effort to discover the bacteriological or virological cause of such illness; and (3) to study the effectiveness of influenza vaccine prophylaxis.

When the study is completed, some five to six thousand persons will have been vaccinated each with a single dose of one of four monovalent, oil-emulsified influenza vaccines. The fiscal year 1952 program was a pilot study to develop epidemiologic and laboratory procedures and techniques.

Dr. Bell and his colleagues have found that the vaccine used in this study produced much fewer local and general reactions than have been experienced in previous studies with non-oil-emulsified vaccines. As compared to the latter, a much higher proportion of persons -- over 95 percent -- developed antibody response to the vaccine and in much higher titers, and these antibodies have persisted for a much longer time. This holds promise for persistence of protection from a single dose for more than one year.

Influenza Information Center. The Influenza Information Center of the World Health Organization influenza study program in the United States is part of the activities of the Section on Epidemiology. Current reports of specific laboratory diagnoses of influenza are received from regional and collaborating laboratories and summarized for publication in the weekly Communicable Disease Summary of the National Office of Vital Statistics, which is widely distributed to health authorities in this and other countries and to the WHO.

During the winter months of 1952, influenza B was locally prevalent throughout the United States, but the death rate was not increased. A total of 89 isolations of influenza B virus and 608 serological diagnoses of influenza B were reported by the 55 participating laboratories.

Sectional Research Program. A major share of the responsibility for the Public Health Service's Sectional Research Program in microbiology has been located in the Section on Epidemiology. This program is supporting, through grants-in-aid, various original investigations on infectious diseases of man which may be important in national defense. It also attempts to develop better collaboration between research centers and official health agencies.

A total of 31 research projects were supported through this program in the last 18 months. In addition, supplies of diagnostic reagents for certain viral and rickettsial diseases were furnished to participating laboratories for investigation purposes and as a stockpile for emergency use.

In the future, the Sectional Research Program will also encourage research investigation by official health departments and the training of workers in specialized methods, in cooperation with other branches of the Public Health Service and the Federal Civil Defense Administration.

LABORATORY OF TROPICAL DISEASES

The activities of this Laboratory in the field of tropical medicine continue to center around basic research on the parasitic tropical diseases. Such diseases are of increasing importance to the United States because of our military operations, increase in world travel, and various assistance programs abroad. They also influence our national economy by reason of the extensive commercial ties which the United States maintains with tropical countries. Because of their chronic and debilitating nature, these widely prevalent diseases are of particular economic importance.

The current research program of this Laboratory continues to reflect the increasing emphasis being placed upon fundamental studies on the physiology of parasites and their intermediate hosts, on the biochemical aspects of the host-parasite relation, and on the physiology of arthropod vectors of disease. Such basic information on the life processes of the etiological agents and their vectors is essential to an understanding of the disease-producing potential of the organism and to a rational approach to chemotherapy of the disease. The routine screening of toxicants for the control of intermediate hosts and vectors and of chemotherapeutic agents is being de-emphasized and increasing attention is being given to the chemistry and pharmacology relating to methods of application and modes of action of these agents. Basic laboratory investigations are followed up by field studies conducted in areas where these diseases are endemic. Clinical research plans include studies on amebiasis, schistosomiasis, filariasis, and trichinosis. Specific projects will be discussed below, together with the major accomplishments of the past year.

Foreign Field Studies

In cooperation with the Pan American Sanitary Bureau and Health Department of Guatemala, studies on onchocerciasis are being conducted to determine the epidemiology of the disease in Guatemala, distribution of vectors, development of the parasite in the fly, development of effective chemotherapeutic methods, and development of measures applicable to control. Distribution of the disease and vectors has been determined and identification keys to the vectors have been prepared. Characters have been discovered by which the developmental stages in the fly can be identified. Several hundred chemicals have been tested for larvacidal effect and pilot studies conducted on the use of these compounds. This study will be terminated at the end of fiscal year 1953.

Tropical diseases in Liberia are under investigation in a cooperative project being carried out with the Technical Cooperation Administration, Health Department of Liberia, and American Foundation of Tropical Medicine. These studies, directed by Dr. Thomas Burch of NMI, deal with diagnosis, and treatment of malaria, trypanosomiasis, filariasis, and schistosomiasis, with emphasis on the biology and ecology of the intermediate hosts and vectors. Surveys have indicated areas with the following disease incidence: malaria 58 to 100 percent; trypanosomiasis 19 percent; and schistosomiasis 25 percent. Mosquitoes of the Anopheles gambiae-A. melas complex are dominant malaria transmitters, with the latter species mainly restricted to the dry season and the former to the rainy season. A gambiae showed a malaria infection rate four times that of A. melas.

Research on schistosomiasis is being conducted in Brazil in cooperation with the Pan American Sanitary Bureau and the Health Department of Brazil. Two NMI staff members, Dr. Louis Oliver and Dr. C. G. Dobrovolny, serve on this project. The study is designed to develop effective methods for the control of schistosomiasis by investigating the biology and ecology of snail hosts and by conducting field tests of potential molluscacides in endemic areas. The influence of water movement, rain fall, types of stream bottoms, and methods of application of the chemicals on various molluscacides has been recorded. This field testing will continue, and studies on the ecology of the snail vectors, begun in November 1952, will be correlated with the results of chemical control tests.

Research on schistosomiasis in British West Africa, in cooperation with the Mutual Security Administration and British Colonial Office, was undertaken to determine the identity and distribution of molluscan intermediate hosts of the disease. Assigned to this project was Dr. Elmer Berry. Large endemic foci of the disease have been discovered and new species of snails have been incriminated as intermediate hosts of the disease. Three new molluscacides have also been found to give excellent results in these areas. A résumé of the 18-month survey has been presented to the Colonial Medical Research Council in London. This study was terminated in July 1952.

In cooperation with the Pacific Tropical Disease Foundation, an investigation of filariasis was carried out in Tahiti to study the epidemiology of the disease and to determine its mosquito vectors and their ecology and biology for the purpose of developing effective control procedures. This work, terminated in July 1952, was in charge of Dr. Leon Rosen. The chief and subsidiary vectors have been identified, and attacks of acute filarial fever were found to be markedly reduced by desensitization with Dirofilaria immitis antigen. Five of the seven local species of mosquitoes have been found capable in some degree of carrying local strains of the parasite to maturity. An extensive mosquito survey was made on all of the six inhabited Marquesas Islands.

Helminthic Diseases

Investigations of the diseases of man caused by worm parasites are being conducted under the direction of Dr. Eloise B. Cram. Current interest is centered on pathogenicity, behavior in various hosts, modes of transmission, cycles of development, morphology, metabolism and growth requirements of the parasites, and on diagnostic methods. Results of continuing work on the effect of cortisone on the cellular and immune response to infection indicate that cortisone influences the susceptibility and refractoriness of experimental animals to infections with some of the nematodes. Some degree of acquired resistance to *Schistosoma mansoni* infection has been demonstrated in mice. Hematological studies on schistosome-infected mice have continued, and the eosinophil response to a second exposure indicates an allergic type of reaction resulting from sensitivity developed during the initial infection. Pathological changes in schistosome-infected mice varied in single sex infections with the sex of the parasite; in exclusively male infections large numbers of worms localized in the lungs, whereas in animals infected with female schistosomes most of the worms localized in the portal system. A difference in susceptibility of geographic strains of snails to infection with *S. japonicum* has been found comparable to that previously reported for *S. mansoni*. Work of a similar nature has been recently started with *S. haematobium* and its intermediate hosts.

Preventive Measures

The objectives of this section, which is headed by Dr. T. H. Tomlinson, Jr., have been the development of methods for schistosomiasis control through the destruction of the snail intermediate host and the development of methods for treating water and food for the destruction of eggs or cysts of pathogenic parasites. During the past year over 500 compounds have been tested for their ability to kill snails under controlled laboratory conditions. On the more promising compounds, studies were conducted on the safety and ease of handling, solubility, dispersal, residual effect, influence on organic matter, and effect on other aquatic life. Methods for quantitative chemical determination of two compounds have been developed, and these procedures have been adapted for use by field personnel. Sodium pentachlorophenate has been found to kill snail eggs as well as the adult snail. The concentration of this chemical has been found to fall gradually to 75 percent of its original value in 14 days and to 20 percent in 54 days after introduction at 0.5 p.p.m. into impounded water.

At the request of the Army, a study was set up in July 1952 to evaluate the efficacy of a newly designed contact clarifier in removing amebic cysts from raw water. This study has provided information as to the efficacy of this procedure for removal of amebic cysts, and also inferential data regarding other pathogens more difficult to test directly. Future work on the destruction of amebic cysts will be confined to requests from defense agencies, while studies on molluscacides will be largely directed toward cooperative studies on mode of action, resistance, and improvement in methods of application and analytical determinations.

Medical Entomology

Work in this section under Dr. Paul A. Woke is directed toward the accurate identification of disease-carrying arthropods, the determination of arthropod reaction to environmental factors with a view toward ultimate improvement in control procedures, and the determination of the mode of action of DDT and other toxicants on insect vectors. The attraction of the human body for Aedes aegypti has been found to be slightly reduced by the ingestion of chlorophyll and the use of commercially prepared hexachlorophene soaps, and definitely reduced by the diversion of exhaled CO_2 from the air stream contacting the mosquitoes.

A. aegypti have been found to be capable of retaining their eggs for at least 90 days after the first blood meal and of depositing viable eggs up to the 40th day. The activity of intact and semi-isolated hearts of mosquitoes is not affected by DDT, and the pupal covering has been shown to be more resistant to penetration by DDT than the covering of larvae or adults. Convulsions of DDT-poisoned mosquitoes are directly correlated with glycogen depletion in the insect.

Studies are being continued on the blood-feeding habits of arthropods with reference to the utilization of the blood in egg production, on the effect of diet upon development of resistance, on the determination of the relative sensitivity to DDT of various tissues and organ systems, and on the relationship between biological changes within the mosquito and its response to stimuli.

Epidemiology

During the past year this unit has been concerned with the determination of the factors influencing the epidemiology of amebiasis, intestinal helminthiasis, toxoplasmosis, and malaria.

Since there is no known treatment for toxoplasmosis, a disease which is now becoming increasingly important, the unit has also undertaken extensive studies on the chemotherapy of this disease in experimental animals. The effectiveness of several drugs against toxoplasmosis in mice has been shown. Daraprim combined with sulfadiazine shows a synergistic effect, and this combination constitutes the most effective experimental treatment yet found.

The use of malaria in treating neurosyphilitics continues to permit the maintenance and study of strains of human malaria. Tissue stages of Plasmodium falciparum have been found in human liver biopsies, and Korean vivax malaria has been demonstrated to be readily transmitted by native mosquitoes. A strain of vivax malaria imported from the South Pacific has shown more of the characteristics of ovale malaria.

In a study carried out in cooperation with Federal Bureau of Prisons, it has been shown that Endamoeba coli is easily transmitted to human volunteers by drinking water and less readily by flies. Studies on a large southern rural population revealed prevalence of amebiasis of 10.5 percent, which was correlated with size of family and degree of fecal pollution of premises but not with pollution of water supply. A resurvey of a rural area in central Tennessee showed a prevalence rate of 22 percent in 1952 compared with a 40 percent rate in 1930.

Protozoal Diseases

Under the direction of Dr. Charles W. Rees, basic studies continue to be carried out on the protozoan parasites of the digestive tract, on *Trichomonas vaginalis*, on *Toxoplasma*, and on trypanosomes and leishmania. While studies at Notre Dame University are incomplete, they indicate that the germ-free gut of guinea pigs does not become infected with amebas following inoculation of bacteria-free amebic cultures. Symbiosis has been demonstrated *in vitro* between *E. histolytica* and single species of bacteria. Metabolic studies on *Trypanosoma cruzi* have revealed the presence of several enzyme systems. The development of drug resistance in one strain of trypanosomes has led to changes in the pattern of infection produced in certain laboratory animals. Studies of toxoplasmosis in animals have revealed that dogs and cats with asymptomatic infections do not show parasites in the blood or feces (thus it is not likely that they play an important role in transmission); strain virulence can be modified by passage through mice but not through chick embryos; parasites have been demonstrated after antibodies were no longer demonstrable; and chronic latent infections are not activated by cortisone treatment, X-ray irradiation, or spleenectomy. Work will continue to be directed toward investigations with germ-free animals and studies on cultivation, growth requirements, mechanism of drug resistance, enzyme systems, and metabolic pathways of these protozoa.

Chemotherapy

Studies in charge of Dr. G. Robert Coatney are largely directed toward two major objectives: basic investigations on the synthesis, pharmacology, physiological disposition, excretion, and mode of action of chemotherapeutic agents in experimental animals, a systematic drug screening program in the search for new chemicals, and field trials of selected compounds against such diseases as amebiasis, malaria, and schistosomiasis.

Using antimalarials as tools in studying modes of drug action, it was found that folic acid antagonists reverse antimalarial activity of sulfonamides and chloroguanide; sulfonamides and triazine metabolites of chloroguanide are not synergistic; closely related antimalarials fail to exhibit cross-resistance; and quinacrine activity in vitro cannot be reversed by any known normal metabolite. In the drug screening program, standardized test procedures are developed and an accepted drug selected as the standard of reference. Eight compounds have been found to have significant amebicidal activity in the guinea pig during the past year. Procedures have been established for satisfactorily testing compounds against schistosomiasis in mice. Daraprim given in a single dose is completely prophylactic against malaria in the chick. An incidental finding of interest was the slight but significant alteration in the course of mouse leukemia by concurrent rodent malaria.

At the request of the Army Research and Development Board and in cooperation with the Federal Bureau of Prisons, a study of the therapeutic efficacy of certain compounds against *vivax* malaria in prisoner volunteers was undertaken. As a result of this and concomitant studies in Army installations, primaquine has been adopted by the Army as the drug of choice for the cure of *vivax* malaria. Investigations on Daraprim have shown that as little as 0.8 milligram per patient per week in a single dose will produce complete malaria suppression; suppressive cures are obtained on a single weekly dosage of 25 milligrams; single 25-milligram doses will control an acute attack, although action is slower than with chloroquine. Toxicity of the pernicious anemia type resulted when 25 milligrams were given daily for 7 weeks, but upon stoppage of the drug recovery was complete without medication; no toxicity was observed when single weekly dosages of 25 milligrams were given. It is expected that this cooperative study will be terminated by September 1953.

Physiology

This section, headed by Dr. Theodor von Brand, deals with the basic physiological processes of pathogenic parasites and their intermediate hosts and vectors. Current studies are designed to furnish information which will serve as a foundation for a better understanding of drug activity and of the appearance of drug resistance. Studies on arsenic resistance in trypanosomes have shown for the first time that metabolic changes are involved in the resistance to organic arsenicals. These studies are now being extended to include inorganic arsenicals in order to determine whether resistance is directed primarily against the organic moiety of the drug or against arsenic. The metabolism of trypanosomes is now being studied to determine the physiological differences between the blood-stream form and the insect form of this protozoa. Studies on the intermediate metabolism of the snail Australorbis glabratus have revealed several enzyme systems, thus providing a basis for the study of the mode of action of molluscacides, one of which has already been shown to produce definite metabolic changes in the snail. During post-anaerobiosis of snails, some acids are excreted while another part is apparently oxidized. Schistosomiasis infection in the snail changes the latter's anaerobic metabolism. Studies on respiration of various species of mosquitoes indicate that sex and species influence the rate of oxygen consumption. The working ability of Trichinella-infected rats is reduced during both the acute and chronic stages of the infection.

Clinical Immunology

In this section, which is in charge of John Bozicevich, studies are undertaken on the development of specific and sensitive antigens for the diagnosis of parasitic diseases (also cooperative studies on bacterial diseases), on the mechanisms of the phenomenon of immunity, and on the biological activity as elicited by parasites in the different hosts. It has been found that the complement fixation test and the flocculation test detect approximately at the same time the first detectable amount of antibody in Trichinella-infected rabbits. An intradermal antigen showing considerable sensitivity has been developed for use in the diagnosis of trypanosomiasis. The newly developed flocculation test has proven sensitive in trichinosis, brucellosis, and tularemia, and good results have been obtained in schistosomiasis and filariasis. Preliminary work with trypanosomiasis has appeared to be satisfactory, but additional work is required on stabilizing the antigen. Studies continue on the adaptation of the flocculation test to the rapid identification of pathogenic agents isolated from contaminated water and air. Future work will be concentrated on this study and also on the development of rapid and accurate diagnostic procedures for leptospirosis and toxoplasmosis as well as on the use of the flocculation test in the detection of specific antibodies during the course of various controlled experimental infections.

LABORATORY OF BIOLOGICS CONTROL

The Laboratory of Biologics Control (W. G. Workman, Chief) is responsible for the administration of the Biologics Law, which is directed at assuring the public of safe, potent, and sterile biological products such as serums, toxins, antitoxins, human blood and blood derivatives. This is achieved through licensing manufacturing establishments as well as the specific products involved.

Licensing is contingent upon the manufacturer meeting and maintaining certain standards and is insured by periodic inspection of establishments and continuous check of manufactured biological products through the submission of samples and testing records to this Laboratory for control testing and inspection. Minimum requirements for each product are revised from time to time, as scientific advances are made in the field. Standard biological preparations are issued for use of those concerned with the manufacture of biological products. As in the past, the relationship of this Laboratory with licensed manufacturers continues to be excellent, and control is achieved by a process of cooperation rather than of policing.

Demands upon the technical and administrative resources of this Laboratory have continued heavy because of the expansion of the National Blood Program involving the licensing and inspection of Red Cross Regional and Defense Blood Centers.

Studies of Serum and Infectious Hepatitis

These studies are under the direction of Dr. Roderick Murray and have two main objectives. The first is to investigate transmission of viral hepatitis by whole blood or any of its derivatives, such as plasma, albumin, and gamma globulin. The second objective is to determine the effects of various diets on the recovery and convalescence of hepatitis patients.

Because efforts to propagate the virus in animals have failed thus far, inoculation studies using human volunteers have been carried on, using materials which have been subjected to a variety of chemical and physical agents. An example of this is irradiation with ultraviolet light. Studies are also being conducted to determine if the virus is "carried" in the blood stream of others. In cooperation with Dr. Lawrence Kilham of the Laboratory of Infectious Diseases, an attempt is being made to grow the virus in animals by tissue culture methods. Funds for the hepatitis project have been supplied by the Armed Forces Epidemiological Board.

Findings and conclusions thus far indicate: 1) that ultraviolet irradiation of plasma cannot be relied on to inactivate the agent of serum hepatitis; (2) that certain blood fractions prepared by the alcohol fractionization method appear to be free of the agent of serum hepatitis; 3) that some chemical agents seem to inactivate this virus under experimental conditions; 4) that some individuals are "carriers" of the virus even though apparently well; 5) that the virus is much more resistant to heat than was previously thought, and; 6) that diet may be an important factor in the treatment of hepatitis.

Reference Standards for Biologic Products

Most biologics cannot be standardized by chemical or physical means, making it necessary to test their effects in relation to standard preparations. The function of this project, directed by Dr. J. W. Hornibrook, is to provide the standard preparations for the use of manufacturers and others engaged in standardizing biologics. It is through this research that uniformity of potency is established throughout the country. Much painstaking and responsible work is required to insure issuance of correct standards. The list of standards is continually changing because of the development of new ones and improvement on old ones. Thirty-five standards or controls are now maintained.

Sterilization of Blood and Blood Derivatives

The major objective of this investigation, conducted by Dr. J. T. Tripp, is to develop methods of controlling the quality and safety of blood and its products. This involves the study of production and control techniques to determine the relative importance of each of the factors thought to influence quality and safety. The immediate objectives are to: 1) determine the incidence of hepatitis transmission through plasma transfusions; (2) develop an improved method of plasma irradiation; (3) determine the effect of irradiation on plasma proteins; 4) compare methods of blood collection; and, 5) determine the cause of changes in plasma-reconstituting solution during storage.

Results to date have demonstrated that commercial plasma irradiated by all three types of irradiators has transmitted hepatitis. It was also shown that five HEP irradiation and heat alter plasma protein markedly.

Biologics Control Tests

The purpose of this project is to evaluate the samples and test records of each lot of every licensed biological product that requires official release. This entails conducting tests for potency, safety, and sterility on samples of such products. In addition, studies are made to improve existing methods of testing and to develop new methods for which there is a need. Cooperative studies are also carried out with the World Health Organization and with other laboratories engaged in biologics studies.

Rabies Virus and Vaccine

This project, directed by Dr. George A. Hottle, concerns investigation of methods of preparing and testing rabies vaccine. Studies on the separation of the paralytic factor in brain tissue from the virus are continuing. The use of agents other than ultraviolet light for inactivation of the virus is being investigated; also a change in the method of potency testing has been adopted and this information transmitted to vaccine manufacturers. This new potency test appears to supply a means of direct comparison of potencies of different vaccines on a statistical basis. Results thus far indicate that it may be possible to remove 75 percent of the allergic encephalitis from the vaccine without losing any potency.

Arsenicals Control Tests

This unit is primarily concerned with the control testing of arsenical compounds released for commercial distribution. A number of limited, long-term studies on the therapeutic effectiveness of arsenicals alone and in combined therapy with penicillin, with respect to the development of resistance, have been under way. A second function is the testing of products for pyrogenicity. Studies are also being made to correlate the pyrogenicity of blood products, as determined by the animal test, with the results obtained by clinical administration. During the past year it was shown that hemolytic factor present in normal human plasma which induces delayed thermal response with hematuria is not of pyrogenic origin; also that clinical experience demonstrates that the pyrogen test in rabbits offers a reliable means of eliminating to a large extent materials likely to induce pyrogenic reaction following human infusion.

Bacterial Toxins

Dr. Sarah E. Branham is in charge of three studies concerning diphtheria, bacillary dysentery, and meningitis. In connection with diphtheria toxins, new techniques have been worked out for evaluation of toxoids and antitoxins at various levels, using seven-day-old chicks rather than guinea pigs and rabbits. It is hoped that these techniques will help determine why antitoxins are not always effective and why diphtheria sometimes occurs in immunized individuals. An effort is being made to discover whether toxins other than the primary ones are formed by diphtheria bacilli, and if so, what their role in clinical diphtheria may be. A study is also being made of late paralysis and cardiac death due to diphtheria toxin. This syndrome in guinea pigs suggests the one that occurs in late stages of clinical diphtheria in people. The histopathological aspects of this problem are being investigated in cooperation with the Pathology Laboratory of NIAMD.

In the work on bacillary dysentery, it has been found that cultures occur in three phases -- I, II, and R. It has been demonstrated that phase I is highly virulent and antigenic, whereas II and R are lacking in these properties. Results thus far indicate that phase I is almost exclusively involved in acute infections, whereas II is preponderant in convalescents and carriers.

Current meningitis studies are directed toward a correlation of various classifications of the meningococcus. The work involves bacteriological and serological comparison of representative groups of strains. A serological study on the epidemiology of meningococcus infections is also being conducted.

Influenza and Poliomyelitis

Studies on influenza viruses isolated in epidemics and outbreaks in various parts of the world are continuing in an effort to determine the effectiveness of present vaccines and to improve them. This work is in charge of Dr. Bernice Eddy. Primary methods used are the standard serum-virus neutralization test, the hemagglutination-inhibition test, and the use of embryonated eggs for virus propagation. Significant this past year is the fact that only type B strains were isolated and that they were similar to those isolated in 1950 and 1951. The similarity is great enough to preclude any necessity of substituting a new B strain in the present vaccines.

Another study now under way and receiving increased emphasis concerns developing practical, satisfactory methods for standardizing immune serum globulins for poliomyelitis antibodies and for evaluating poliomyelitis vaccines. Preliminary standards have been set and tests are being made for uniformity of potence for the three types of virus using animal inoculation, complement fixation, and tissue culture methods. The most significant results to date concern the working out of a satisfactory globulin-type 2 virus neutralization test in mice and complement fixing antigens for types 1, 2, and 3 viruses from the brain and spinal cord of cotton rats.

Hemophilus Pertussis and Hemophilus Influenzae

The purpose of this unit, directed by Dr. Margaret Pittman, is fourfold: to assure that pertussis vaccines are adequate and as uniform as possible in potency; to reduce post-vaccination reactions; to learn why *H. pertussis* produces a disease that has so many anomalous clinical features; and, to further develop therapeutic agents. Continuous activity has been directed toward maintaining adequate vaccine standards, close inspection of potency of vaccines, and advising manufacturers on procedures of preparation and further studies of therapeutic agents. Effort has also been directed toward analyzing available data on fatal reactions following vaccination to try to determine a common factor for attack. Work has continued to center on the mouse histamine sensitizing factor of pertussis vaccine and the action of antihistamines and adrenal fractions on the phenomenon and the effect of the sensitizing factor on anaphylaxis.

ROCKY MOUNTAIN LABORATORY

The Rocky Mountain Laboratory (Carl L. Larson, Chief) continues to emphasize a basic research approach to studies on virus and rickettsial diseases of particular importance to public health in the Western United States. During the past year this Laboratory has made an encouraging start on its biophysics studies, which required considerable attention to technical problems, and has strengthened its biochemical investigations. Specific research programs are outlined below along with major accomplishments of the past year and plans for the future.

Arthropod Vectors Section

Problems Relative to Arthropod-borne Diseases. Serological evidence of Western equine encephalitis, Rocky Mountain spotted fever, brucellosis, and a psittacosis-like agent was found by Dr. C. B. Phillips in a Nevada study of a localized jack rabbit die-off. No tularemia was found in these animals, although several virulent strains of *Bacterium tularense* were recovered from *Dermoentor parumapertus* collected from uninfected hares. Recovery of strains of Colorado tick fever from this tick and from *Ornithodoros lagophilus* probably bears upon the epidemiology of this disease. Studies made to clarify the relationship of Indian tick typhus rickettsioses to its vectors and to other rickettsias reveal that while dog ticks are known to become naturally infected, it is more difficult to transmit this agent through ticks than it is to transmit the agent of Rocky Mountain spotted fever. Indian tick typhus and boutonneuse fever seem to be closely related or perhaps identical. A study of special interest, because of the implication of helminths as vectors of infectious agents, has shown that the agent of "salmon poisoning disease of dog" is a rickettsia-like organism carried by fluke parasites. The disease is fatal to dogs, but no other available animals are susceptible.

Biology of Ticks. The general biology of 26 species of ticks of the genus Ornithodoros and their relation, if any, to the tick-borne spirochete strains known to be causative agents of relapsing fevers are currently under study by a unit headed by Dr. Gordon E. Davis. Disease agents of spotted fever, tularemia, Q fever, rat-bite fever, and rickettsialpox are being investigated. Since the present classification of relapsing fever spirochetes is inaccurate and unsatisfactory, research is being directed toward clarification based upon the general biology and ecology of the various "species" under study.

Arthropods as Vectors of Disease. This project, directed by Glen M. Kohls, is devoted to accumulating knowledge of arthropods, especially ticks, leading to an understanding of their role as disease vectors. Cooperative studies of Colorado tick fever with the virus unit have continued. Data to date suggest that the incidence of the disease is higher than formerly believed and that it is probably the most common tick-transmitted disease in the western United States. Current studies on the geographical distribution of Colorado tick fever virus in Dermacentor andersoni will be expanded in 1953 to include animal reservoirs of this disease. The presence and persistence of B. tularense in certain local streams has been established. Contamination of natural waters with this organism, tularemia in aquatic animals, and their role in human infection continue under investigation.

Mosquitoes and Mites as Vectors. Culex tarsalis is the most important mosquito in the epidemiology of western equine encephalitis. Intensive studies of this mosquito offer the most promising approach to the ecology of the virus involved. Its colonization is essential to laboratory investigations of virus-mosquito relationships. In this study by Dr. James M. Brennan, a colony has been established and is thriving in its fifth generation. In collaboration with the Virus Unit, Dr. Brennan attempted to isolate western equine encephalitis virus from C. tarsalis obtained from a study area in North Dakota. The low incidence of virus in these mosquitoes was in contrast to results obtained with lots obtained from California in which 42 virus isolations were accomplished. In another study, evidence indicated that Aedes aegypti mosquitoes cannot retain virus for more than two days after infective feedings. This study has not been completed. Two new species of chiggers were described during the past year and knowledge of host-parasite relationships obtained.

Parasitic Agents. In a study by Dr. William L. Jellison of tick-borne tularemia in sheep, residual tularemic infection in lambs 30 to 60 days after illness indicated that lambs going to market may be infective for man. Studies of tularemia in water and in semi-aquatic mammals were continued in the past year. Infection was demonstrated in one new area of Montana. An epidemic on Kodiak Island and the Pribilof Islands, diagnosed by others as leptospirosis, was reinvestigated and the original diagnosis was not substantiated. Infectious viral jaundice was a more likely diagnosis.

Virus and Rickettsial Section

Viral and Rickettsial Diseases. The objective of this unit, headed by Dr. Carl M. Eklund, is to establish the reservoir of infection and vectors of importance in arthropod-borne virus diseases of importance in the Western States. In a study of Colorado tick fever, virus has been isolated from blood specimens taken from patients living in eight Western States and from D. andersoni ticks collected in four States. Present data indicate that in D. andersoni ticks, hereditary transmission plays a minor role in the maintenance of the virus. Virus has been isolated from ticks other than D. andersoni but their importance in the maintenance of virus is unknown. In the encephalitis study, serologic surveys have shown marked differences in the geographical distribution of antibodies to the western equine and St. Louis viruses, which indicate important differences in their maintenance and spread. During non-epidemic years, the low incidence of western equine viruses suggests that mosquitoes are an unimportant factor in the maintenance of virus during such periods. A new virus has been isolated during three summers from A. trivittatus mosquitoes collected in North Dakota. Antibodies to this virus have been found in human and equine sera, but human disease due to this virus has not been recognized.

Epidemiologic Studies of Viral Diseases. In one study, Dr. Cecil R. Reinstein is investigating factors influencing the relationship of age and sex to susceptibility of mice to western equine encephalitis. The objective is to determine the basis of susceptibility and resistance to animal infection. A tissue culture study involving isolation of viral agents from field specimens and neutralization tests has as its objective the further development and use of practical, rapid, and inexpensive procedures for diagnostic confirmation and research studies.

Tularemia Vaccine Studies and Epidemiology of Botulism. Vaccine studies, directed by Dr. J. Frederick Bell, are aimed at evaluating tularemia vaccines for human use and to determine the relationships of virulence and immunity, using tularemia as an example of a disease caused by gram-negative organisms. In another study, in cooperation with the Fish and Wildlife Service, an effort is being made to determine the epidemiology of botulism in wild fowl and to study methods of prevention. A method to maintain continued toxigenicity of Clostridium botulinum has been devised.

Studies of Q Fever and Leptospirosis. The pathogenesis of Q fever following exposure of cattle to infectious aerosols has been investigated by Dr. Herbert G. Stoenner. Cattle infected by aerosol sprays regularly developed CF antibodies, but irregularly manifested chronic disease. Later studies show that young open heifers, heifers in the last trimester, adult cows in late pregnancy or just post-parturition, and adult cows in midlactation all developed CF antibodies, but only animals in the second and third groups shed C. burnetti. These experimental data tend to duplicate observations on naturally infected herds in California. In connection with leptospirosis, a capillary tube agglutination test employing an antigen which remains stable for a year has been developed. Studies with this test will continue.

Epidemiology of Spotted Fever. In this study by Dr. E. John Bell, toxins have been demonstrated in the ten strains of spotted fever rickettsia tested and the factors involved in toxin production evaluated. Toxicity is not related to virulence. Another study to determine response of volunteers to vaccination against spotted fever indicated the value of booster doses of vaccine. One booster dose was shown to be as effective as three. Results obtained in a study of immunologic relations between strains of the spotted fever group suggest that the toxin-neutralization test may aid in epidemiologic studies and in the classification of the responsible rickettsiae.

Leptospirosis Study. This investigation, directed by Dr. Karl R. Reinhard, has the following objectives: determination of animal reservoirs; survey of human populations for undiagnosed leptospirosis; study of experimentally infected animals; development of immunization measure; study of comparative serology and development of better cultivation techniques. Most progress has been made with the first phase of the project, in which serological confirmation has been obtained of the existence of leptospirosis in cattle in 14 States. Swine leptospirosis was shown to be present in four States. The implications of this work are that a huge reservoir of a human pathogen exists. The investigator believes that extension of this work will demonstrate it throughout the nation.

Q Fever Investigations. In these studies of Q fever vaccines, Dr. Lauri Luoto has used experimental laboratory animals and dairy cattle to test the safety of vaccines which might be employed for the control of Q fever in dairy cattle. Potent vaccines capable of stimulating complement-fixing antibodies are not deleterious to the health of bovines. Actual vaccination of immigrant herds, native herds, and problem herds has just started and no results are available yet. A capillary tube agglutination test, employing stained antigens, has been devised for the diagnosis of Q fever in cattle. Simple and specific, the test can be employed as a field tool.

BIOPHYSICS AND BIOCHEMISTRY SECTION

Biophysical Characteristics of Bacteria and Viruses. The objective of this unit, headed by Dr. C. C. Shepard, is the study of the morphology of intact bacteria and viruses and their component parts. The work centers around the electron microscope, but corroboration and clarification is constantly sought with other technics such as electrophoresis, ultracentrifugation, and immunological and chemical methods. During the past year a study of B. tularense was begun, and as soon as this is finished other organisms will be investigated. Because much time thus far has been spent on investigation of technical aspects, it is hoped that the study of other organisms will move somewhat faster.

Biochemical, Physiological and Immunologic Aspects of Gram-Negative Pathogens. In a study of the metabolism of Coxiella burnetti, employing living organisms from infected yolk sacs and measuring the enzymatic activity by conventional methods, Dr. Richard A. Ormsbee has shown that the major part of the classical carbohydrate oxidation system is present. A study of the mechanism of antibiosis active against Q fever has shown that in descending order of effectiveness, terramycin, aureomycin, and chloromycetin are effective in the treatment of Q fever. It was also shown that there is a constant relation between the size of the infectious dose and the therapeutic dose, and that the action of aureomycin and terramycin is rickettsiostatic. In connection with tularemia vaccine, purification and fractionization of antigen has resulted in isolation of a highly active antigen which is now being characterized.

Bacterial and Mycotic Diseases Section

Immunologic Studies of Organisms. The objectives of these studies, conducted by Dr. Carl L. Larson, are to investigate antigens capable of producing immunity toward Gram-negative organisms. Major findings include the following. A booster dose of soluble antigen from B. tularense given three months after primary vaccination produces greater immunity than does a comparable amount of antigen given at intervals of two to three weeks. Antigens from P. pestis grown at 30° C. or 37° C. are capable of immunizing guinea pigs against infection when incorporated into Freund's adjuvant. The toxic effect of killed *Brucella* for mice is enhanced when killed tubercle bacilli are added. Volunteers vaccinated with soluble antigen from *B. tularense* develop antibodies against this organism, with no unfavorable response noted. Among vaccinated individuals, four cases of tularemia occurred; these were very mild and not typical of laboratory infections.

Studies of Gram-Negative Pathogenic Bacteria. In these investigations, by Dr. B. H. Hoyer, three main groups of organisms have been studied: *Brucella*, *Pasteurella pestis*, and *Leptospira*. The objectives are to achieve better understanding of nutritional, enzymatic, and immunologic properties of these organisms by developing suitable growth media, by fractionation and purification of antigens, by testing enzymatic activities, and by animal protection tests. Studies of antigenic cross reactions of *Brucella* ureases *in vitro* reveal cross reactions among urease-containing preparations from *Br. abortus*, *Br. suis*, and *Br. melitensis*. By a simple precipitation procedure involving lowering the pH of soluble antigens prepared from *P. pestis*, it is possible to separate the antigen mixture into toxic and nontoxic fractions. A defined medium for the growth of the free-living *Leptospira biflexa* has also been developed. Organisms grown in this medium are being used to study some of the growth characteristics of leptospirae. Application of this knowledge to pathogenic leptospirae is planned.

Immunologic and Physiologic Aspects of the Pulmonary Mycoses. Dr. Samuel B. Salvin's studies concern the epidemiologic, diagnostic, and therapeutic aspects of various diseases caused by fungi, with special reference to histoplasmosis. In cooperation with certain investigators, serums are being examined for precipitins, complement-fixing antibodies, and neutralizing antibodies. It appears that a combination of these tests not only establishes the diagnosis of histoplasmosis but aids in prognosis. White mice may be actively immunized against infections with *H. capsulatum* with acetone-dried cells, and studies are under way to test whether or not other fungi can be employed to produce specific immunity.

Diarrheal and Dysenteric Diseases. These studies by Dr. K. C. Milner concern the pathogenesis, immunity, chemotherapy, and epidemiology of infections with bacteria of the Salmonella group. It was found that administration of certain antibiotics, even at non-toxic levels, appears to increase the susceptibility of chicks to infection with *Salmonella typhimurium*. Traditionally prepared vaccines confer on mice a very low order of protection when challenged with *S. enteritidis* and *S. typhimurium*. The implications of this finding are being explored, particularly with regard to their bearing on typhoid immunization. Another project concerned improvement of methods for establishing the specific etiology of rat-bite fever. A stable soluble antigen has been prepared from disintegrated cells which, within limits of present experience, reacts specifically in complement-fixation and precipitation tests. Its practical utility is to be tested as suitable materials become available. The unit has also shown that cultures of the *Streptobacillus* may be preserved by lyophilization.

Serology of Diseases Caused by Infectious Agents. The objective of this unit, directed by Dr. David B. Lackman, is to support the research program of units in the laboratory by performing serologic tests for the diseases under investigation. This includes a diagnostic service for clinical specimens. The study of the antigenic structure of members of the spotted fever group of rickettsiae and the psittacosis group of viruses represents an important continuing project of the unit. Findings in the past year include detection of human cases of psittacosis in Twin Falls, Idaho. The presence of this disease had not been suspected. A procedure is under study in which complement fixation is utilized in the assay of tularemia soluble antigens. Good results have been obtained in the early stages of this work. The agent isolated elsewhere as the cause of bovine encephalitis has been shown to be a member of the psittacosis group of viruses. Thus far no relationship between bovine encephalitis and human disease has been shown.

Culture Studies of Infectious Agents. In addition to its research objectives, this unit, in charge of R. K. Gerloff, is responsible for maintaining strains of rickettsiae and viruses in embryonated eggs, to supply mass inoculation procedures for other units, and to prepare antigens for experimental use. The unit has isolated a virus from Haemaphysalis leporis-palustris ticks by direct inoculation into embryonated eggs; it is believed to be an insect virus with pathogenicity only for the developing chick embryo. Other findings include the demonstration that Ornithodoros moubata ticks can be infected with Q fever by direct feeding on the membranes of infected embryonated eggs. The virus of Colorado tick fever was also shown to be neurotropic and, when cultivated in the embryonated egg, the central nervous system tissue of the embryo is the only rich source of the virus.

Pathology of Infectious Diseases. To support the various research projects of the laboratory, this unit, headed by Dr. W. J. Hadlow, provides pathologic examinations of animal material from both natural and experimental disease conditions. This entails a detailed microscopic study of a wide variety of tissues from many species of animals. During the past year the unit reported an extensive interstitial myocarditis had been found associated with experimental Spirillum minus infections in several wild and laboratory animals. The agent of bovine encephalitis was shown to cause a fibrinous peritonitis, similar to the serositis found in the natural disease, but no encephalitis in experimentally infected guinea pigs.

LABORATORY OF CLINICAL INVESTIGATION

In preparation for the opening of the Clinical Center, this laboratory (Norman B. McCullough, Chief) has completed its plans for the Microbiological Institute's clinical research program to be conducted in the new facility. The program will concentrate on infectious and parasitic diseases of public health importance.

Based on a coordinated laboratory--clinical approach, this program will seek to improve existing, or to develop new, methods and techniques for the diagnosis and prevention of infectious diseases, and to develop new or more effective methods of treatment, control, or cure. Specific approaches will be employed on selected diseases along such lines as the early recovery, isolation, and classification of etiological agents; the development of detectable antibodies; and therapeutic trials of certain drugs and antisera.

In collaboration with the Research Foundation of Children's Hospital, Washington, D. C., clinical studies of respiratory viral diseases were conducted in the past year by a scientist of the Laboratory of Clinical Investigation. The viral isolation and other laboratory work were carried out by the Laboratory of Infectious Diseases. This project will be transferred to the Clinical Center after the facility is opened. The results of the past year's study include recovery and identification of Coxsackie group viruses new to the Washington area; evaluation of the use of the suckling mouse for diagnosis of herpes simplex infection and refinement of the technique using early passage neutralization tests; and further clarification of the diagnosis of herpangina and differentiation from gingivo - stomatitis.

Diseases which will be studied when the Clinical Center begins operations include brucellosis, rheumatic fever, histoplasmosis, hepatitis, trichinosis, amebiasis, schistosomiasis, and filariasis.

EXTRAMURAL PROGRAM

The Extramural Programs Branch of the National Microbiological Institute is responsible for the administration of research grants and research fellowships in the broad field of microbiology. This program is coordinated with the Institute's own research activities, and a continuous review is maintained of disciplines and fields covered.

The present extramural program covers such fields as viral, rickettsial, spirochetal, and protozoal diseases, and investigations dealing with fungi. The program also includes the sponsoring of fellowships to provide training for scientific personnel interested in microbiological research. In addition, research grant support is implementing a nation-wide sectional research program for biological warfare defense, the objectives of which are to expand and to strengthen the existing civilian facilities for the specific diagnosis of outbreaks of diseases not ordinarily included in routine laboratory techniques, and to encourage original research by independent investigators on diseases which may be of importance to biological warfare defense.

A total of 244 research grants amounting to $2,177,813 is currently being supported by the National Microbiological Institute. Forty-two fellowship awards were also made in fiscal year 1952.

A survey completed in the past year indicated that a considerable amount of research in microbiology is being supported by the grants programs of other Institutes at NIH. This reflects the fact that many chronic diseases have their origin in infectious diseases. The survey showed that 172 research projects amounting to $1,738,769 were being supported by other Institutes, of which the microbiological component was computed at $1,337,903. Examples of projects in this category include those dealing with septic shock, endocarditis, rheumatic fever, oral microbiology, genetic studies, joint inflammations, and certain central nervous system diseases.

During the past year the Tropical Medicine Study Section of the Division of Research Grants sponsored several conferences on toxoplasmosis, a parasitic disease in which medical science has shown increasing interest in recent years. As a result of the conferences, diagnostic facilities for toxoplasmosis have been established at the Communicable Disease Center of the Public Health Service in Atlanta. These facilities are available to health departments throughout the nation.

NATIONAL INSTITUTE OF MENTAL HEALTH

R. H. Felix, Director

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NATIONAL INSTITUTE OF MENTAL HEALTH

July 1, 1951 - December 31, 1952

Introduction

Mental illness continued to present one of the Nation's most serious public health problems -- with estimates indicating that there are some 650,000 persons in mental hospitals, and several million others with severe emotional disturbances. Under the provisions of the National Mental Health Act of 1946, the National Institute of Mental Health has continued its efforts toward reducing the toll of mental and emotional disorders through its programs of intramural research, research grants and fellowship awards, training grants, and technical assistance and grants-in-aid to the States to develop community mental health programs.

With the opening of the Public Health Service Clinical Center planned for the near future, the Institute began preparations to make the best use of the expanded facilities for laboratory and clinical research. Dr. Seymour S. Kety was named Associate Director in Charge of Research for the combined basic research programs of the National Institute of Mental Health and the National Institute of Neurological Diseases and Blindness, and Dr. Robert A. Cohen was appointed Director of Clinical Research for the National Institute of Mental Health. New sections are being organized in intermediary metabolism, enzymology, cerebral metabolism, cellular physiology, functional neuroanatomy, cytoarchitecture, animal and human behavior, special sense physiology, and anthropology.

Research studies at the Institute during the past 18 months have produced new information on the physiological activities of cellular nucleic acids, the physiology of the cerebral cortex, the basic neural mechanisms operating in the spinal cord, the relation between aging and changes in the nervous system, and the meaning of spontaneous verbal behavior in psychiatric interviews. The Section on Addicting Drugs, at Lexington, Ky., made important gains in its studies of the addictive properties of narcotic drugs and the personality of addicts. A cooperative project with the Worcester (Mass.) Foundation for Experimental Biology has produced methods of analyzing urinary and blood steroids of a reliability previously unobtainable.

The 145 independent projects which received support through research grants covered a wide range: anatomy, biochemistry, and physiology of the nervous system; normal child development; distribution, frequency, and genetics of mental illness; psychological processes; cause and diagnosis of various mental and emotional disorders; evaluation of methods of prevention and treatment, and relationships between social stress and mental illness. Special grants were made to support projects concerned with specific program needs of the Institute. Seventy-two new research fellowships were also awarded.

In supporting training programs, the Institute followed the principle that quality of teaching was of first importance. During the past 18 months, 383 grants were made to support graduate teaching in the psychiatric disciplines; 1,343 stipends were awarded to individual trainees, and 40 medical schools received grants for the psychiatric education of some 14,000 students.

Evidence of the growth of State and community mental health programs is found in the increase of funds contributed from State and local sources to match Federal grants-in-aid. The ratio is now three dollars for each Federal dollar. States and communities put increased emphasis on providing psychiatric orientation for persons in related professions, such as teachers, social workers, and public health nurses. States sought assistance from the Institute and its regional consultants in making their community mental health programs more effective. The Institute's demonstration clinic in Prince Georges County, Md., showed results indicating the importance of offering a community a variety of consultative and educational services in addition to clinical services for individuals.

The proposed draft act for the hospitalization of the mentally ill, which has served as a guide to State legislatures and has resulted in improvements in State laws concerning the mentally ill, was brought up to date in line with experience, and reissued. At the request of five States, comprehensive surveys were made of 14 mental hospitals and schools for mental defectives.

In determining the best use which might be made of the Institute's facilities and professional services, particular attention was given to rehabilitation of the mentally ill, drug addiction among minors, aging, juvenile delinquency, industrial mental health, and mental deficiency. Efforts were continued to help the States develop meaningful systems of reporting statistical data concerning the mentally ill. The Institute also prepared informational material in response to the interest of the public in mental health problems, and helped the States develop their informational services.

RESEARCH GRANTS AND FELLOWSHIPS BRANCH

The Research Grants and Fellowships Branch is responsible for administering the extramural grant and fellowship program of the National Institute of Mental Health, including administration of the Mental Health Study Section. As in the past, this program receives assistance from and coordinates its activities with the Division of Research Grants.

It is now five years since the first research grants were awarded under the National Mental Health Act. Feeling that this was an appropriate time to review the accomplishments of the research grant program and the direction in which it might move in the future, a comprehensive analysis was made of the grants awarded to date, for consideration by the Mental Health Study Section and the National Advisory Mental Health Council.

From July 1, 1947, through September 1, 1952, slightly over $5,000,000 was awarded in support of 165 projects. Analysis by problem area showed that heaviest support had been given to research into (a) the etiology, symptomatology and pathology of mental illness, (b) development or evaluation of treatment methods, (c) normal child development, (d) studies of the nervous system, and (e) the relation of environmental stress to mental health and illness. Forty-four percent of the applications for "basic" research were approved, compared to 27% of "clinical" applications. However, clinical applications received 58% of the funds, compared to 33% for basic research.

Analysis by disorder showed that 42% of the funds were spent on projects dealing more or less directly with a psychiatric disorder, 22% on "adjustment problems" of various kinds, and 20% on basic research with no immediate or direct application to any disorder. The remaining 16% was spent on neurological and miscellaneous other disorders.

Analysis by methodology showed that a minimum of 50 categories had to be used in classifying the projects. The largest number of approved projects employed psychological methods (62). Projects utilizing social science methods (42), and those utilizing biological, chemical or pharmacological methods (36) were next in frequency. Twenty-two projects were essentially studies in psychiatric treatment methods. Relatively few projects (18) were supported in interdisciplinary research, which may be an indication of the difficulty of this type of approach.

This analysis was used by the Mental Health Study Section and the National Advisory Mental Health Council in considering the problem of priorities in mental health research. Lengthy discussions by both groups, and a study of suggestions on priority areas by present and former members of both groups, indicated considerable similarity between these suggestions and the actual distribution of funds in the past 5 years. It was also the consensus that it would probably be harmful to progress in mental health research and to the investigators working in this field to establish a formal list of priority areas. The present system of reviewing individual applications on their merit was felt to be preferable. It was agreed, however, that more attention could be paid to "gap" areas and to encouraging investigators from other than strictly psychiatric or psychological disciplines to concern themselves with problems of mental health and illness.

One way of accomplishing this is through the activities of the Study Section and Council. During the period covered by this report, a committee of the Mental Health Study Section was established, on the suggestion of the Council, to explore the contributions which might be made to the problems of mental health and illness by the biological and biochemical sciences. This committee has held a first meeting and has arranged a second one to consider various approaches to the problem of regional localization of function in the brain, with plans for future meetings on other specific topics.

Another committee of the Study Section which has become active in this period is the committee to evaluate completed projects. This is an expression of the continuing concern of the staff and its advisory bodies to evaluate the research grant program and to determine ways in which it might be strengthened or reoriented to meet the changing needs and emphases in the field.

The furtherance of research is aided not only by support of direct research activities but also by the support of research conferences, at which investigators are given the opportunity of exchanging ideas and information and obtaining new insights and leads from other disciplines and investigators. Three such conferences were held in 1952, supported by the National Institute of Mental Health. The first of these was the final conference on psychosurgery, chaired by Dr. Fred A. Mettler, and attended by psychiatrists, neurologists, surgeons, and others actively working in this field. The second was a conference on the effect of early experience on mental health, held at the Jackson Memorial Laboratory in Bar Harbor, Maine, under the chairmanship of Dr. J. P. Scott. The third conference consisted of a series of meetings held in conjunction with the annual meetings of the major professional societies concerned with problems of mental health, to discuss the problems which arise in carrying out interdisciplinary research in the mental health field, to compare methods and techniques which have been evolved, and to point the way toward more effective research in which the utilization of teams of workers from various disciplines is required.

In the past 18 months, 145 separate research projects have received support through research grants. These projects, as in the past, cover a wide range of problems concerned with the field of mental health and illness: basic studies on the anatomy, biochemistry, and physiology of the nervous system, normal child development, the epidemiology and genetics of mental illness, and basic studies of psychological processes; studies of "experimental neurosis" in animals; clinical studies on the etiology, diagnosis, and symptomatology of a wide variety of mental disorders, including schizophrenia, childhood disorders, psychosomatic disorders, organic psychoses, and epilepsy; evaluation of such therapeutic and preventive techniques as psychotherapy (individual and group), counseling, milieu therapy, and psychosurgery; and clinical-environmental studies on the relation of social stress to mental health and illness.

The results of a number of these projects, or of those formerly supported, are now beginning to appear in published form. One such publication is a volume entitled "Communication, the Social Matrix of Psychiatry," by Drs. Jurgen Ruesch and Gregory Bateson, in which modern communication analysis is applied to the problems of psychiatry such as the schizophrenic process in which interpersonal communication is seriously disturbed. Another significant contribution has been made by Dr. Fritz Redl and David Wineman in their two books, "Children Who Hate" and "Controls from Within." These investigators have studied the nature of the disorganization and breakdown of behavior controls in emotionally disturbed children and have developed a number of group therapy techniques for treating such children.

The importance of play in helping to develop emotionally healthy children and in correcting incipient conflicts and tensions is discussed in detail in the book, "Understanding Children's Play," by Ruth E. Hartley, Lawrence K. Frank, and Robert M. Goldenson. Play therapy has long been recognized as a valuable tool in dealing with disturbed children and this work represents a detailed study of the values to be derived from well directed play activities. The increasing use of psychosurgery in the treatment of mental disorder has made its evaluation timely and important. "Psychosurgical Problems," edited by Dr. Fred A. Mettler, is the second volume to appear, reporting on the results obtained by a group of medical scientists and clinicians from Columbia University's College of Physicians and Surgeons and the New Jersey State Hospital at Greystone Park.

The problem of manic-depressive psychosis has received increased attention in recent years. Important to further work in this field is a knowledge of the large body of work that has gone on in the past. This task has been greatly aided by the recent publication of a book entitled "Manic-Depressive Psychosis and Allied Conditions," by Dr. Leopold Bellak, in which the data of over 1,200 articles are reviewed in a systematic fashion.

The studies of Dr. Alfred Stanton and Dr. Morris Schwartz at Chestnut Lodge, Rockville, Md., entitled "psychiatric and sociological study of a mental hospital ward," represent the first adequate attempt scientifically to scrutinize the psychological processes by which an institutional environment and institutional personnel affect mental patients. Since these widely published studies have opened the eyes of psychiatrists, nurses and hospital administrators the country over to the possibilities of research in this area, there is no doubt that they will provide stimulation for a number of years to come for a general expansion of research upon mental hospital treatment.

Sixty of the projects supported in this period received support from the National Institute of Mental Health for the first time, many representing the extension of our program into new and significant areas of research. Dr. Franz Kallmann's studies of the significance of genetic factors in the diseases of old age, including the senile psychoses, are now being supported at the N. Y. State Psychiatric Institute under a five-year grant, continuing the support initiated in 1945 by the Rockefeller Foundation. Dr. Kallmann's studies of the role of genetic factors in various types of illness by the twin-study method are well known and have had a significant impact on current thinking. Another project in the field of aging is that of Dr. Ewald Busse, at the University of Colorado, who is studying the effect of aging on the central nervous system by means of the electroencephalograph.

Today, about 5,000 psychiatrists in this country - as well as many other physicians - spend a part or all of their time treating patients by a process known as psychotherapy. There is no doubt as to the value of this treatment, but only recently have modern scientific methods been focused upon this process. The Research Grants Program of the NIMH is now supporting a number of projects in this complex area. Drs. Bordin, Dittman, and Raush, at the University of Michigan, have received a 3-year grant to develop new methods for measuring a few dimensions of psychotherapy scientifically, dimensions similar to those most psychiatrists employ today without knowing precisely how reliable they are. Dr. O. Hobart Mowrer, at the University of Illinois, received a 1-year grant to develop quantitative methods of measuring change in the course of psychotherapy. The relative effectiveness of group and individual therapy with various types of patients is being studied by Dr. Jerome Frank at Johns Hopkins University, a continuation, in part, of Dr. Frank's earlier studies for the Veterans Administration.

Evaluation of several different types of therapy with children has also been initiated at a number of institutions. Dr. Ronald Lippitt at the University of Michigan, following up the findings of a previous grant from the National Institute of Mental Health, is attempting to develop techniques for changing the group acceptance and social adjustment of emotionally disturbed children in classrooms and camp groups. Dr. Redl has received a grant to study the effects of specific group games and activities on the emotional adjustment of disturbed children. And Dr. Bruno Bettelheim, following up his previous studies on institutional treatment of emotionally disturbed children, has now received a grant to study what personality characteristics are required in persons working with disturbed children in an institutional setting.

In the area of psychotherapy with children, there has been a great need to study some of the theories upon which most treatment of disturbed children is based. Dr. Sears' studies at Harvard University promise to demonstrate the manner in which the child's disturbed actions in the play interview are related to the parents' habitual ways of acting with the child and should provide solid direction for child psychiatrists.

A new type of shock therapy has recently been developed for psychiatric patients, known as photic stimulatory therapy. Dr. George Ulett has received a grant to evaluate this treatment method at Washington University, St. Louis.

Convulsive shock treatment today is the commonest short-term successful physical therapy for the severely disturbed mental patient. Despite the fact that this treatment has been in daily use in every section of the country for over 10 years, heretofore no appropriate method of studying the exact physical effect of convulsive therapy upon the brain has been developed. Dr. Ulett's present studies will record for the first time quantitative measurement of the changes in the brain waves produced during convulsive therapy.

The role of ACTH and cortisone in disease and illness is receiving much attention these days and many studies are under way. Two additional studies in this field are now receiving support from the NIMH. Dr. Leo Samuels at the University of Utah has begun a study of adrenocortical function in schizophrenia and the influence of emotional conflict and electroshock treatment on adrenocortical activity. Dr. Leslie Phillips, working in collaboration with the Worcester Foundation for Experimental Biology and Medicine, is studying the relation of social adjustment to psychological and adrenal cortical reactions to stress at the Worcester State Hospital.

Recent developments have permitted the direct electrical stimulation of the brain and the recording of electrical activity directly from the brain. These studies have contributed much useful basic information on brain activity and offer some hope of developing new therapeutic approaches to mental illness. Two grants were awarded recently for studies utilizing these methods. Drs. Harry Solomon and William Chapman, at the Harvard Medical School, are carrying out physiological studies of the relation between the electrical activity in the frontal and temporal lobes of the brain to automatic regulation and emotional expression in man. Dr. Robert Heath and his associates at Tulane University are attempting to correlate the electrical activity of the brain with the accompanying biochemical alterations and emotions in the patient.

A number of other important studies have been initiated in the fields of psychosomatic disorders, mental health in industry, epidemiology of mental disorder, juvenile delinquency, child personality and development, and communication in psychiatric patients, but space does not permit their listing.

In addition to the award of research grants, significant support has been given for the training of scientists in research techniques by means of research fellowships. One hundred and eight fellows were supported during this period, including the award of 79 new fellowships, to assist in the training of young investigators in such fields as psychiatry, neurology, neurophysiology, biochemistry, and the social sciences. In this way, the future availability of research scientists in the many fields which may contribute to problems of mental health and illness is furthered.

TRAINING AND STANDARDS BRANCH

During the period July 1, 1951, to December 31, 1952, the Training Branch continued its efforts in the direction of developing and stimulating improvement in the field of mental health education. There remains a serious deficit in the number of qualified specialists to provide the variety of mental health services needed. These needs range from service in mental hospitals, in clinics, to the field of public mental health and the field of mental health administration. As the implications of mental health become more clearly defined, greater demands are being made to provide services that will insure better health. This has placed a strain upon those mental health specialists available, making for a highly competitive market for their services.

The Training Branch of the National Institute of Mental Health is striving to help train as large a number of psychiatrists, clinical psychologists, psychiatric social workers, psychiatric nurses, and specialists in the field of public mental health as possible to meet these demands. For this reason, a substantial amount of support is provided for the purpose of assisting individuals in getting specialized training in any of the areas mentioned above.

In spite of the urgent need of even greater numbers of personnel, it is felt that the quality of training is of primary importance. In other words, the quality of training should be placed ahead of quantity of personnel to be trained. This implies that mental health personnel should be trained to that point of competency which will enable them to provide the various kinds of services that will be demanded by an ever changing society. Therefore, a considerable effort has been directed toward improving or extending mental health education. This has been done through support of teaching programs in the field of psychiatry, clinical psychology, psychiatric nursing, psychiatric social work, and public health, as well as through assisting professional organizations in the disciplines mentioned above to review critically the design and content of teaching so that personnel receiving such training are kept abreast of the requirements and demands of a changing social structure.

During the period July 1, 1951, to June 30, 1952, grants were made to 42 medical schools totaling $600,119. During the period July 1, 1952, to December 31, 1952, grants totaling $584,143 were made to 40 medical schools. These grants serve to extend, improve, or develop undergraduate psychiatric education for approximately 14,000 students in medical schools. These grants help to extend psychiatric teaching throughout all four years of the medical school, to extend or improve upon teaching during the clinical years, or to provide for more extensive supervision of the students. The purposes of this program are twofold -- to better prepare the student to handle emotional problems encountered in a general practice or to lay a more substantial background for further specialized training in psychiatry.

During the period July 1, 1951, to June 30, 1952, a total of $3,670,373 was available to support graduate programs in the disciplines of psychiatry, clinical psychology, psychiatric nursing, psychiatric social work, and public health. Of this amount, $2,180,714 was available to support 194 teaching grants and $1,489,659 to provide 701 stipends in support of individual specialized training. During the period July 1, 1952, to December 31, 1952, a total of $3,515,197 was available to support 189 teaching grants and 642 traineeships in the above-mentioned specialities. In recapitulation, during the period July 1, 1951, to December 31, 1952, $2,882,296 was available as stipends to support individual training of 1,343 individuals and $4,303,274 to provide for 383 teaching grants, making a grand total of $7,185,570.

In addition, limited funds were available for a number of special institutes and conferences concerned with the study of the design and content of mental health curricula in the fields of psychiatric nursing, clinical psychology, psychiatric social work, and in the field of teacher training. In recognition of the seriousness of the problem of alcoholism, funds were made available to bring together interested people concerned with research and the administration of this problem at a State level in order that a more concerted and active program in this field could be developed. During the period July 1, 1951, to December 31, 1952, there were 11 such institutes for which grants amounting to $57,986 were awarded.

These included grants to Montana State University for an institute for the training of clinical psychologists; Harvard University School of Public Health for a conference on mental health teaching in public health training programs; Rhode Island State Health Department for a mental health institute of public health nurses; San Jose College for a workshop in vocational counseling for rehabilitation workers; to Teachers College of Columbia University and to the Menninger Foundation for institutes on vocational rehabilitation of the psychiatrically disabled; Colorado Department of Public Health for an institute on alcoholism; National State Conference on Alcoholism for clinical conferences on alcoholism; University of Michigan for a conference on the implications of current theory and findings in human relations and human development for the preparation of teachers; Board of Control for Southern Regional Education to develop psychological services in eight southern States; and Yale University for a mental health institute for health educators.

COMMUNITY SERVICES BRANCH

One of the primary resources for help in steering the course of the Community Services Branch program during the past year and a half has been the Community Services Committee of the National Advisory Mental Health Council. This committee whose 15 members are authorities in health, education, and welfare from outside the Federal Government met twice during the 18 months covered in this report.

One of its important actions was to receive a subcommittee report on Mental Health Implications in the Civil Defense Program and to recommend that "the National Advisory Mental Health Council advise the Surgeon General to contact the Federal Civil Defense Administration, requesting that due consideration be given to the psychological or emotional aspects of civil defense preparation, and that full utilization be made at all levels of mental health facilities and personnel, and that he consider offering the Civil Defense Administration the full assistance of the Public Health Service to the end that mental as well as physical health, be protected insofar as humanly possible."

The committee also discussed and emphasized the value of and need for more mental health consultants in the Regional Offices in view of the increasing complexity of problems related to the developing mental health programs in the States.

It recommended that States be urged to provide more funds for training mental health personnel who are needed to meet the demands of the program which is being spread into the ongoing services and activities of many community agencies.

It also discussed and urged acceptance of the concept of a mental health center which would concern itself with the total mental health needs of a community, including involvement in broad community planning to provide the framework within which mental health concepts and principles would be integrated into all community services and activities.

The subcommittee further recommended the appointment of "a subcommittee on evaluation, to study and report on the areas of research which are needed, preferably in a priority order, in the community services field."

Financial resources available to the Community Services Branch for continuing assistance to the developing community mental health programs (other than institutional care) were $3,100,000 from new appropriations for grants-in-aid to States in the 1952 fiscal year. In addition, there remained in the State treasuries $180,000 from the 1951 fiscal year. Thus, for this fiscal year a total of $3,280,000 was available to the States. The minimum grant for any State in fiscal year 1952 was $19,200.

During the year a total of $12,243,000 was spent on State and local programs, of which only $3,243,000 were Federal dollars. It is interesting to note that the $12,243,000 spent for community services programs is only 2 percent of the funds spent by the States each year to provide hospital care for the mentally ill.

In the reports from the Institute's regional consultants, there is a positive and healthy overtone expressed about the effectiveness of activities carried on cooperatively with other agencies through joint planning and operation.

Significant evidence of growth is found in the increase of funds from State, local and private sources which are available to match the Federal grants under the National Mental Health Act. The ratio now is three State, local and private funds dollars to one Federal dollar. For the past two years, all of the States and Territories have had a mental health program.

While the programs in States vary a great deal, there seems to be a common core based upon program administration, educational services for the general public, early treatment in the clinics, inservice training, consultation services to community agencies, support of professional personnel in accredited training, rehabilitation, and studies in special areas.

It was apparent that a shortage of State level personnel has been a drawback to program development, especially in the Midwestern, Southwestern and Southern States. In 18 States and Territories, $204,000 were budgeted for stipends for 94 trainees. This is considerably less than last year and results from inadequate funds to support trainees and at the same time maintain services.

Opportunities for State and Regional mental health personnel to get together have been provided through meetings arranged by the regional consultants. Such meetings have been held in Boston, Chicago, Dallas, Kansas City, Washington. Program content common to all was discussed.

In 46 States and Territories, 334 mental health clinics received part or all of their support from grant-in-aid funds. One hundred sixty-eight of these clinics have been started since 1947 and 14 of these began operation during the last fiscal year. In addition to providing diagnostic and treatment services for about 100,000 patients, these clinics provided consultation and educational services to other community agencies, such as the health department, the schools, and the welfare department. These consultative and educational services distribute help to a far greater number of people and at the same time provide opportunities for the clinic staff to help the workers of other agencies gain understanding and skill in handling many emotional and behavior problems.

As part of the educational program most of the States distribute such literature as the "Pierre the Pelican" series for mothers of the first born which is still very popular. The "Psychiatric Bulletin" for the physician in general practice has reached a circulation of 26,000 in 13 States. Motion pictures are still the most popular item in the field of public education and information. The radio, and television to a lesser extent, are being used by most States and local communities having a mental health program.

Since the use of films is increasing it seems essential that more information be obtained about their effectiveness. A project has been started in the Institute in which the Community Services Branch is participating in the evaluation of these films in terms of accuracy of information, audience selection, and the probable receptiveness of the film.

Consultative services on mental health education are being expanded through a public health educator now on the Community Services Branch staff. During this first year, the consultant visited seven of the Regional Offices. On these visits, the health education consultant with the regional mental health consultants gave assistance to nine States and two Territories, by participating in workshops and institutes for mental health, welfare, and school personnel, and meetings with health educators. In addition, the consultant participated in two summer workshops for school administrators and teachers.

When the National Mental Health Act was passed in July 1946, there were only three public health nurses with psychiatric training employed in public health agencies or schools of public health. At present, 120 mental health nurses are employed by community public health agencies primarily in the supervision, consultation, or teaching of nursing personnel.

There has been a notable increase of interest and numerous requests for advice concerning the establishment of psychiatric units in general hospitals. Recommendations were made concerning improvement in the care and treatment of mental patients, in physical facilities of hospitals and in their administrative methods. General interest on the part of hospitals has increased in the fields of geriatrics and treatment of alcoholism.

At the request of State administrations the hospital consultation service made complete surveys of 14 mental hospitals and schools for mental defectives in Kansas, Kentucky, Florida, Montana, and West Virginia. Consultation on special problems was given to State agencies and to 14 hospitals in Virginia, Vermont, Oregon, California, Louisiana, and Pennsylvania.

The Prince Georges County Mental Health Clinic, College Park, Maryland, continued to function as a demonstration project seeking new methods of developing community mental health programs. One activity directed toward achieving this objective is the attempt to demonstrate that a flexible administrative policy permitting shifting emphasis on clinic, consultation and education services better meets the clinic's responsibility as an integrative agency as well as its responsibility to individuals who are in need of psychological or emotional help. This project was initiated by the simple administrative decision that direct therapeutic or diagnostic services would not be offered to individuals unless they were referred by some other professional source. In addition, the professional agencies referring patients are required to contact some member of the clinic staff prior to the referral of the individual, furnishing pertinent data about the case and discussing the needs both of the individual patient and of the agency making the referral before the clinic accepts responsibility for seeing the patient. These pre-referral contacts have helped the other community agencies in utilizing the clinic's resources and have been especially valuable in guiding cases referred by the school system.

A study was completed dealing with a survey of the nature and extent of mental health problems presented by a group of ninth-grade children in the public school system in an effort to develop a method for identifying those who might need psychological assistance. The subjects of the study were 810 ninth-grade students. The results of this study are being published and will be available in reprint form. 1/

The Community Services Branch furnishes a psychiatrist, a clinical psychologist and a secretary to the D. C. Juvenile Court Guidance Clinic. Consultation, diagnostic services, physical examinations, and psycho-therapy in selected cases, are the main functions of the clinic. In addition, participation in the inservice training program for social workers and field placement for the training of a graduate student in clinical psychology have been a part of the clinic's activities. Clinic conferences for pediatric residents of Children's Hospital have also been held.

The Community Services Branch staff has maintained a continuing relationship with the Office of Vocational Rehabilitation, directly and through the Professional Services Branch, to bring about an increase in services to patients discharged from mental hospitals. Rehabilitation services for discharged mental hospital patients have been expanded in eight States chiefly through the efforts of the regional consultants. In Virginia, for example, special funds have been appropriated to provide special training for rehabilitation counselors so that they may work effectively with discharged mental hospital patients. The regional mental health consultants are working with less active States to extend their programs and are participating as leaders and resource persons in workshops, institutes, and conferences for program, hospital, and other administrators, supervisors, and rehabilitation counselors.

The initial project in a long-range research program preliminary to developing community mental health screening techniques has been completed under a special grant to the University of Illinois and the next phase has been started.

Members of the Community Services Branch staff have visited a number of school projects designed to integrate mental health principles and practices into the curriculum. The Branch anticipates the completion of a report and guide lines on mental health in schools to be available to regional staffs in the near future.

1/ Ullmann, Charles A., "Mental Health Screening of School Children," Public Health Monograph. (in press)

At the request of the Federal Civil Defense Administration, the National Institute of Mental Health agreed to have one staff member serve one-half day per week with the Federal Civil Defense Administration as consultant on mental health aspects of the civil defense program.

The report on Mental Health Implications in Civil Defense Programs, prepared by the Subcommittee on Civil Defense with a staff member of the Community Services Branch serving as Executive Secretary, was presented to the Community Services Committee at the October 1951 meeting. The Committee recommended to the National Advisory Mental Health Council that the report be published and distributed to the Public Health Service regional offices, State mental health agencies, regional Federal civil defense administrative officers, State and local civil defense authorities and additional distribution as indicated by the Federal Civil Defense Administration. The Council approved this recommendation on February 14, 1952. The report was submitted to the Federal Civil Defense Administration in March 1952 for consideration and clearance for publication.

At the October 1951 meeting of the Community Services Committee, a Subcommittee was appointed to study and report on evaluation studies of community mental health activities. The Community Services Branch designated a staff member to serve as Executive Secretary. This committee will prepare a report to include: (1) a review of evaluation studies reported in the literature; (2) identification and description of studies now in progress and (3) recommendations as to need for further research in certain areas with some indication as to priority order. It is anticipated that this study will involve at least a two-year period.

Branch activities relating to alcoholism continue to be directed toward assisting State and local programs and promoting conferences, institutes, and other measures for the exchange of relevant information. Three projects were supported by NIMH grants during the period of this report; namely, the completion and publication by the Yale Center of Alcohol Studies of a comprehensive survey of current activities relating to alcoholism; an Institute held in Colorado for medical and public health personnel; and a conference on therapy in Richmond, Virginia.

The Headquarters and Regional staff participated as faculty in over 200 mental health institutes for inservice training of health, welfare, education, and vocational rehabilitation personnel.

The fourth annual meeting called by the Community Services Branch for chief social workers from State mental health programs was held in Chicago, May 23-24, 1952. Present at the meeting were 25 of the 32 psychiatric social workers now working in State mental health programs and representatives from the Regional Offices and the National Institute of Mental Health.

The first meeting of chief psychologists in State mental health programs called by the Community Services Branch was held in Chicago, August 30, 1951. Twenty-two psychologists, representing 13 States, three Regional Offices, and the National Institute of Mental Health, considered problems related to suggestions for improving the developing State mental health programs.

Sixty-three mental health nurses (including 6 graduate students) met for a two-day session in Atlantic City in June to learn what methods, techniques, and experiences are the most appropriate teaching tools in helping nurses develop relationship skills.

PROFESSIONAL SERVICES BRANCH

The Professional Services Branch continued its activities of planning and evaluation, budget review, and the provision of consultative services within the Institute, to other parts of the Service, and to nongovernmental groups. There were also several new developments in the Branch's activities.

The Branch was given responsibility for the development and coordination of the special grant program of the Institute. These grants are made to certain individuals or organizations who are especially qualified to carry out projects to support specific program needs of the Institute.

Administrative procedures for awarding special grants have been developed. The Professional Services Branch assists any staff member of NIMH in the development of special grant proposals. The Branch coordinates activities in this area and attempts to study the nature of the program needs of the Institute for which special grants would be helpful. It may also initiate such grants.

During the last year and a half, the Professional Services Branch has expanded the concept of program planning to include program development activities in areas of significance for the entire Institute. These areas are usually ones which also interest other constituents of the Federal Security Agency and other Government departments or agencies. The Professional Services Branch approaches each of these problems with the intention of summarizing the current state of knowledge and nature of activities in the field, of establishing clearly the relevance of mental health concepts and techniques to this problem, of developing pilot studies or activities in the field, and of working out techniques whereby the present knowledge and possible program solutions developed can be integrated into the Institute's operating programs. The following areas of activity are currently receiving attention:

1. Rehabilitation of the mentally ill. Dr. Richard Williams has had responsibility for this special area of work in which the Community Services Branch cooperates. A study of the literature and of current activities concerned with the rehabilitation of mental hospital patients was completed by Mrs. Charlotte Schwartz while she was a temporary employee of the Branch.

The Institute also has cooperated with the Office of Vocational Rehabilitation to make possible three institutes, each of two weeks' duration, covering the mental health and psychiatric aspects of vocational rehabilitation. Each State has had an opportunity to nominate at least one person to attend one of these institutes.

A special grant has also been made to Boston State Hospital to study rehabilitation techniques of mentally ill patients in this institution. Close liaison has been maintained by Dr. Williams.

Finally, specific planning has started, looking toward a study of community influences affecting the continued rehabilitation of discharged mental hospital patients.

2. Drug addiction among minors. Activity in this area has been continuing since late June 1951, with Dr. Joseph M. Bobbitt as the responsible

staff member. Three special grants have been made in this field, one to the Chicago Area Project, one to the Bureau of Applied Social Research, Columbia University, and one to New York University. The Columbia project is complete and resulted in the production of two documents: Drug Use Among Adolescents: A Framework for Social Research and Social and Psychological Factors in Opiate Addiction. The latter document has already been published. The third project was initiated in June 1952. Dr. John Clausen, Chief of the Laboratory of Socio-Environmental Studies, has cooperated on these special grants and has served as the liaison officer.

Institute personnel, chiefly from the Professional Services Branch, with the assistance of Dr. Curtis Southard of the Community Services Branch, have worked with the Children's Bureau, Office of Education, Office of Vocational Rehabilitation, Food and Drug Administration, and a representative of the Administrator's Office in developing a statement of Objectives and Guidelines for Community Programs in addiction control. The Regional Offices have assisted by supplying detailed information on the status of the problem in their various regions.

3. Aging. Dr. Lawrence F. Greenleigh spent approximately eight months studying the problem of aging as it is related to mental health. His activities resulted in a document entitled Psychological Aspects of Our Aging Population, which has been well received. As a consequence of Dr. Greenleigh's leaving the Service, Dr. Williams has been given responsibility for continued activity in this field.

4. Juvenile Delinquency. Dr. Donald Bloch has recently been given responsibility for development in this field. He is working closely with the Children's Bureau. Progress has already been made in arriving at an understanding concerning those parts of this general problem area which are primarily the concern of the Institute. Several research or pilot projects are currently under consideration.

5. Industrial Mental Health. Dr. Richard Bell has worked with the Public Health Service's Division of Occupational Health of the Service for more than a year, studying the possibility of developing projects designed to clarify the mental health aspects of industrial health problems. Some review of the literature has been completed and several possible research projects are under consideration at the moment.

6. Mental Deficiency. Work in this area was begun very recently by this Branch. It has received some preliminary consideration from Dr. Carter of the Community Services Branch. Dr. Bloch plans to give it the same kind of consideration that has been given to aging and rehabilitation of the mentally ill.

7. Development of a Long-range Balanced Program for the Institute. Dr. Williams has devoted a great deal of time to this activity. The preparation and revision of this document has had the cooperation of the professional staff of the Institute. In this connection he has visited each Regional Office and has prepared a report on his observations of the role and function of mental health consultants in Regional Offices.

BIOMETRICS BRANCH

During the past year and a half the Biometrics Branch has continued to make progress in the collection and presentation of uniform mental hospital data and in further developing the research possibilities of such data.

The second annual Conference of Mental Hospital Administrators and Statisticians from 11 States, which constitute a "Model Reporting Area" for mental hospital statistics, was held in Washington, D. C., in February 1952 under Institute sponsorship to determine how more adequate data could be obtained on the hospitalized mentally ill and to determine progress in this direction since the last meeting a year ago.

The conference recommended adoption of specific definitions of "first admission" and "resident patient" so that uniformity would exist from State to State and make inter-State comparisons more valid. Also adopted with minor modifications were twelve tabulations suggested in the new "Diagnostic and Statistical Manual of Mental Disorders" which would form the basis for data gathering, not only in the eleven States themselves but ultimately in the other thirty-seven as well.

Minimum standards for a State's inclusion in the Model Reporting Area were set up in order to encourage other States to develop their statistical systems. These standards were: (1) a central reporting system in charge of a professionally trained statistician; (2) adoption of the uniform definitions approved or to be approved by the Model Reporting Area, and (3) annual preparation of at least the minimum number of basic tabulations as recommended by the Area.

Proceedings of the Second Conference of Mental Hospital Administrators and Statisticians are in process of publication and will be made available to the Mental Hospital Authorities in each State.

The Biometrics Branch has during the past year been asked to provide consultative services to various States, particularly Texas, Kansas, Wisconsin, and Minnesota, desiring to set up or to improve reporting systems for their mental hospitals. This should aid in expanding and strengthening the movement toward uniformity and comparability initiated by the Model Reporting Area.

During the period since July 1951 a survey was made of the services and treatment facilities available to mental patients in general hospitals with 50 or more beds and in private mental hospitals throughout the United States. This study is being extended to include all general hospitals with less than 50 beds. For the first time data will be available on a national scale indicating which general hospitals accept mental patients, whether diagnostic or treatment services are available, and in the latter case, what the specific treatment facilities are.

A survey on the extent of the use of psychosurgery in this country was conducted by the Branch under the auspices of the Conference of Psychosurgery and will be published in the Proceedings of the Third Psychosurgical Conference.

The Biometrics Branch has been working with the Prince Georges County Mental Health Clinic at College Park, Maryland, and the District of Columbia

Bureau of Mental Hygiene Clinics in developing record forms and record-keeping systems that would enable the clinic to evaluate its operations and to gather data on a more meaningful basis. A number of States have requested copies of these experimental forms in order to determine the possibility of adoption to their local needs.

In order to determine what communities require additional mental health services and to provide basic information to State, local, and voluntary groups interested in mental health clinic service, the Biometrics Branch is planning to initiate an annual statistical report for collection of uniform data on mental health clinic services. The basic information to be sought by the National Institute of Mental Health will cover geographic areas served, hours per week that the clinic is open, number, age, sex, and diagnosis of persons served, community services rendered, professional staff members and trainees, and sources of funds.

A preliminary draft of the statistical reporting form has been distributed for comment and criticism to all State mental health authorities and to national organizations, such as the American Psychiatric Association, the National Association for Mental Health, the American Association of Psychiatric Clinics for Children, the Community Chests and Councils of America, and also the U.S. Children's Bureau and Veterans Administration. The Biometrics Branch has also held meetings with interested groups in various parts of the country to exchange ideas on the subject.

It is planned to distribute the new reporting forms and instructions early in 1953, in order to have a nationwide report initiated for the fiscal year 1954.

From July 1, 1951 to December 31, 1952, the following reports were published:

"Patients in Mental Institutions: 1948"

"Patients in State Mental Hospitals: 1949," IMH-B52, No. 1

"Patients in Mental Institutions: 1949"

"Maintenance Expenditures in Public Mental Hospitals in Relation to General Revenues of States," Public Health Reports, July 1952, pp. 681-685

"Patients in Public Hospitals for the Prolonged Care of the Mentally Ill: 1950" IMH-B53, No. 1

PUBLICATIONS AND REPORTS SECTION

The Publications and Reports Section of the National Institute of Mental Health continued its efforts to provide material which would help people to understand and seek solutions for the problems of mental illness.

The Section worked with the Institute's professional staff in making authoritative information on mental and emotional disorders available to community leaders, professional workers, and the general public through speeches, articles, pamphlets, films, press releases, and other media. Among the national organizations which received special assistance in preparing educational material for their memberships were the American Association of University Women, the General Federation of Women's Clubs, and the Association of the Junior Leagues of America. A special exhibit was prepared for the Fourth International Congress on Mental Health in Mexico City.

Pamphlets published by the Section in response to numerous requests for information included "What to Know About Drug Addiction," "What You Should Know About Alcoholism," and "Looking Forward to the Later Years." A monthly "Progress Report" was distributed to persons and groups wanting information on new developments in the psychiatric field and in community mental health activities. Individuals seeking advice on personal problems were referred to suitable facilities in their communities whenever possible.

Efforts were continued to assist the States in building up their own film and pamphlet libraries. Members of the Institute's professional staff reviewed films on mental health subjects, and the Section issued a revised edition of the descriptive catalog, "Mental Health Motion Pictures." A second revised edition of the catalog, "Mental Health Pamphlets and Reprints," was also issued.

Writers on mental health subjects for newspapers and magazines were given assistance in obtaining pertinent material. Again this year, the Institute cooperated with the National Association for Mental Health in sponsoring National Mental Health Week, May 4-10. For the first time, support of the Advertising Council was secured in this campaign. Three radio network shows featuring prominent actors were produced for the occasion, and other radio scripts released by the Institute for general distribution were widely used.

A long-range plan was developed to integrate the Section's program with the needs and goals of the mental health movement. During 1953, particular emphasis will be given to the need of training an adequate amount of skilled professional personnel for positions in clinics, hospitals, laboratories, industry, teaching, and private practice. In subsequent years, emphasis will be given to research, community services, and other phases of the mental health program.

LABORATORY RESEARCH: NATIONAL INSTITUTE OF MENTAL HEALTH and NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES and BLINDNESS

July 1, 1951 - December 31, 1952

The past eighteen months have seen the initiation of a combined program in basic research for the National Institute of Mental Health and the National Institute of Neurological Diseases and Blindness under a single associate director. This program is based on a thesis which recognizes that progress in the diagnosis and treatment of nervous and mental disease rests firmly upon a basic understanding of the nervous system through the biological and behavioral sciences. Since it is difficult if not impossible to predict which basic research areas will develop information of practical therapeutic value, a well-balanced program will include representative research in all major areas. It will thus provide an opportunity for contributions from many diverse fields and will utilize profitably the unique facilities of the National Institutes of Health for interchange of ideas and pooling of efforts among the various disciplines. During the past year existing research of the National Institute for Mental Health has been integrated into this program and some progress has been made in initiating some of the newer segments.

In the ensuing year, 1953, a broadening of the intramural program will occur not only in the basic sciences but especially in clinical research in the fields of psychiatry and neurology. The directors of two of these three areas have now been appointed: Dr. Robert Cohen in psychiatry, and Dr. Seymour Kety in basic research. The clinical director for neurology has been chosen and will be appointed in the near future.

The basic research program for 1953 includes the establishment of Laboratories of Neuroanatomy, Neurochemistry, Neurophysiology, Experimental Psychology, and Epidemiology within which most of the present sections will be included. New sections are being organized including sections on intermediary metabolism, enzymology, cerebral metabolism, cellular physiology, functional neuroanatomy, cytoarchitecture, animal and human behavior, special sense physiology, and anthropology. By the close of 1953 the program of basic research will be broad and representative of the most promising areas of investigation, constituted in a manner to offer opportunities and encouragement for the best type of collaborative effort within itself and with the programs of clinical investigation.

Section on Developmental Neurology

This section was organized September 1, 1952, at the University of Chicago where it will remain until the opening of the Clinical Center. The objective of this section is the acquisition of knowledge concerning the development of the complex organizational structure which is the nervous system. Research has been devoted to two aspects of this organization: the integrative principles operating and the respective roles of experience and maturation in the development of the visual system, and an assessment of the importance of the integument in the chemical specification of the cutaneous nerves during development.

An apparatus has been perfected for testing the visual capacities of the cat that seems to be far superior to previous methods in results. This apparatus provides a sensitive measurement of visual capacity that should be useful in many kinds of studies on vision. New data have been added on the developmental stage at which integumental specification of cutaneous nerve becomes irreversibly fixed. Investigation to test conflicting theories of neural organization in the visual cortex has been started.

Good progress has been made on an approach to the location of visual memory traces using as a method of attack, the interocular transfer of monocularly trained habits with transection of various brain commissures combined with different types of brain lesions.

Various modifications of the Rasdolsky, Silver, and Mallory strains for synaptic end-feet have been explored in an investigation of the regulative influence of peripheral upon central nervous connections in development.

Dr. Roger Sperry, chief of this section, has been honored by an invitation to deliver the Hixon Lectures at the California Institute of Technology.

Section on Physical Chemistry

Dr. Alexander Rich, chief of this section, was appointed August 1, 1952. His investigations, which are being carried on at the Gates and Crellin Laboratory of the California Institute of Technology until the opening of the Clinical Center, are directed to elucidating the structure of the desoxyribose nucleic acids, both as regards macromolecular configuration and the detailed spatial orientation of the constituent nucleotides. The ultimate goal of physical and structural studies such as these is the insight which may be obtained into the physiological activities of nucleic acids in the nuclei of cells, since such activities are an intimate reflection of chemical architecture.

Nucleic acids, when complexed with proteins, are considered the fundamental constituent out of which genes and chromosomes are constructed. As such, they therefore occupy a key role in all biochemical systems in that they are believed to direct the metabolic patterns of the cell. In nerve tissue, the importance of nucleotides and nucleic acids in physiological activities has been effectively demonstrated in recent years.

Double refraction of flow has been used as the principal tool for characterizing the macromolecular behavior of nucleic acids. This method is a sensitive index to molecular dissymmetry and leads directly to a parameter related to the length of the molecule. By carrying out studies of this type, configurational changes in the molecule can be observed as the environment is altered.

Finer details of molecular structure have been investigated by an X-ray diffraction study of nucleic acid films. When a beam of monochromatized X-rays passes through matter, it is scattered in such a manner that measurements of the spots of the scattered beam leads directly to inter-atomic distances which exist within the molecules. These distances can in turn be correlated with various possible configurations which the molecule can assume.

In addition to work carried on with nucleic acid films, fibers have been drawn in an attempt to create a partially crystalline orientation of the molecules. If this attempt is successful, it will be possible to obtain a great deal of information concerning the orientation of the constituent nucleotides in nucleic acid.

During this period, the construction of an instrument has been completed. This instrument was designed specifically to carry out double refraction of flow studies on molecules similar to the desoxyribose nucleic acids. Some preliminary experiments have been undertaken which show that the instrument is functioning as expected.

A number of X-ray diffraction investigations have been carried out on various salts of nucleic acids. Using a dried film, the sodium salt of nucleic acid has produced a well defined powder pattern, which has in it the characteristic 3.34 A spacing, believed to be the internucleotide distance. In the acid itself, the diffraction rings produced by this spacing diminish in intensity considerably, while in the cesium salt, this spacing is observed to scatter more intensely. From these facts, we have been able to infer that the phosphate groups themselves are arranged approximately 3.34 Å apart.

Section on Neurophysiology

This section, headed by Dr. Wade Marshall, has continued its work in the physiology of the cerebral cortex and the interesting phenomenon of spreading depression. The past year has seen widespread acceptance of the contribution of this group over the past three years in demonstrating that the widely heralded suppressor areas of the cortex were manifestations of the phenomenon of spreading depression and, as such, merely artifacts. In this regard alone this section may be said to have rewritten an important page in neurophysiology.

During the past year this section has concentrated on an intriguing aspect of spreading depression. There are occasionally abnormal electrical waves, peroxysmal in character, accompanying the spreading depression wave. The possible relation of this to a Jacksonian epileptic march is obvious and has intrigued many investigators.

This group has rounded out adequate proof that excess potassium ion applied over a properly exposed arachnoid membrane will create the conditions necessary for spreading depression and that this is reversible by application of potassium free Tyrode solution. The potassium ion result is not specific for spreading depression. Calcium free and sodium free solutions also create conditions for spreading depression; that is, any ion unbalance in the subarachnoid space is important. Occasionally one sees, instead of depression of the cortical brain wave rhythm, little or no depression, or actual enhancement. The appearance of a travelling excitation rather than depression presents a challenging situation.

It has been found that under chlorolose anesthesia application of excess potassium ion over the arachnoid membrane produces a regular 2 to 4 per second negatively directed discharge. After 10 to 20 minutes of application of this solution a typical depressing type of spreading depression can be evoked. Application of potassium free solution almost immediately produces changes in the excess potassium ion pattern either to reduce it and gradually change it to the normal for chlorolose anesthesia or in some cases to reverse the electrical sign so that the waves are positively directed. It is becoming clear that the distinct changes of activity are during the 15 to 30 minute interval during which ionic equilibrium in the subarachnoid space is being established.

Considerable disagreement and frank confusion exists in the literature concerning the descending motor pathways other than the direct corticospinal. Although the suppressor areas are becoming recognized in general as an artifact of careless technique, their presumed relation to Magoun's brainstem centers for turning motor behavior on and off has not been questioned. Of more positive interest is the anatomical distribution in the brainstem of physiological activity induced in the motor cortex, its somatotopic organization, if such exists, and its relation to actual peripheral muscle contraction as recorded electromyographically.

The general plan is to stimulate the motor and perimotor areas methodically while recording brainstem activity with multiple inserted leads.

Although some strychnine activation may be done in association with or separate from electrical stimulation, it is considered likely that such mass activation would be undesirable in this study. Since the motor area is small and in large part buried in the cat, the major study is to be done in the monkey. Preliminary observations in the cat are planned. Since one of the important experimental questions will be whether activity recorded from the brainstem is mediated by collaterals of the pyramidal tract rather than entirely by a non-pyramidal route, some chronic control preparations have been made. These include unilateral and bilateral pyramidotomy in the medulla. For control of cortical response mediated by the corpus callosum, some unilateral cortical ablations have also been made.

Section on the Spinal Cord

The general purpose of this section under Dr. Karl Frank is the elucidation of the basic neural mechanisms operating in the spinal cord: the excitation of nerve cells and the mechanisms by which their excitation is inhibited or by which they become more excitable. Two principal methodological approaches are employed: (A) The first is the well established technique of observing the reflex electrical responses of peripheral motor nerves to stimulation of various sensory nerves. Inferences about the nature and behavior of the central nervous system are drawn from the distribution of reflex activity over the various motor nerves from the time elapsing between stimulation of a sensory nerve and the appearance of a motor response, and from the alterations in reflex response produced by stimulating two or more sensory nerves in different temporal patterns. (B) The second experimental approach is the new and almost untried technique of recording electrical potentials of nerve cells or fibers with a microelectrode placed inside the cell. This technique differs from (A) above in that the above method records the aggregate response of a large number of nerve fibers while the latter records the electrical behavior of a single cell to the virtual exclusion of that outside the cell. In addition, it permits a measurement of the resting membrane potential of the inactive cell and of alterations in this potential due to stimulation of various peripheral sensory nerves or due to stimulation of the nerve fiber of the cell penetrated. This technique thus provides a method for studying the mechanism by which one nerve cell excites another or inhibits its normal excitation by a third nerve cell.

While it is assuredly a long step from the knowledge of the behavior of single cells in the spinal cord to the prevention or treatment of human diseases, yet such knowledge is necessary for a better understanding of the nervous system itself. The use of the isolated spinal cord permits study of a part of the nervous system in simpler form showing a more stereotyped and reproducible behavior than the higher centers and therefore more readily measurable. The units of the spinal cord, the neurones, are quite similar to those of the brain, and the whole complex behavior of the nervous system results from the combined interactions between pairs and groups of these nerve cells. It is therefore of prime importance to study the basic unit mechanisms of interaction between nerve cells, of excitation and inhibition of one group of cells by another, if we are to arrive at a penetrating understanding of the operation of the nervous system as a whole, whether it is in a normal or a pathological state.

The past year has been devoted chiefly to the development of the technique and construction of equipment necessary for successfully recording the electrical potentials of single nerve cells in the spinal cord with intracellular electrodes. A number of important modifications and improvements have been made in existing techniques. A method for making the fine electrodes has been developed which yields a fivefold improvement in electrode conductivity. In addition, by means of a metallic shield on the fine electrodes and the development of a new circuit, other limiting defects in previously described techniques have been overcome. In preliminary trials the ability of the new electrodes to record faithfully the delicate electrical changes occurring within single cells in the spinal cord has been successfully demonstrated.

Section on Technical Development

This section, under Michael M. Davis, Jr., has two main functions; the primary one being that of a service organization for the biological research program of the National Institute of Mental Health. Secondly, it conducts research of its own on new methods and new techniques of instrumentation, keeping abreast of the latest arts of instrumentation and attempting to make suitable application to the biological sciences. During the past year the section has become formally organized, and considerable growth has occurred particularly in the forms of plans and equipment procurement.

Plans and design work have been under way for some time to develop an integrated system of equipment particularly suitable for neurophysiological research. This is to consist of frequency and sweep generators, delay generators, stimulating units, amplifiers and pre-amplifiers, cathode ray tube presentation, timing mark generators, and associated power supplies. The work already done includes the basic work-up and test of circuitry for base-rate and sweep generators, and the construction of a dual power supply for this equipment. It also includes the procurement of commercially available pulse equipment, which is at present being evaluated for possible incorporation into this equipment. This program has also required the procurement of many components to be on hand for development purposes.

An integrated recording and sound system has been worked out from commercially available, and some locally fabricated, equipment. This system provides two recorders (one for portable use, the other fixed) which can transcribe to one another so that field recordings can be put into standard form for stenographic transcription.

A counting rate recorder was designed and constructed for use in conjunction with radioactivity measurements. This equipment is a digital type recorder which counts impulses from one to any number of hundreds for a predetermined length of time varying from a few seconds to sixty seconds. The results of a count for a particular interval are recorded on an Esterline-Angus instrument.

A considerable part of the work of the section has been devoted to aiding the instrumentation aspects of the Section on the Spinal Cord. This has included the design and construction of a dual beam cathode ray tube unit with a rather unique directly-coupled beam-blanking system, the design and construction of an electrically controlled animal respirator, with an emergency power system so that if, for any reason, the power failed, the respiration of the animal would continue from battery power for a period of hours; thus, protecting both the animal and the experiment from unexpected power failure, the design and construction of two pre-amplifiers, one of which was a conventional battery-operated cathode follower; and the other of which was a quite special very high input impedance amplifier with a feed-back circuit to a driven shield. This latter pre-amplifier has proved most successful for microelectrode work, where resistances may be as high as 100 megohms in situ.

Section on Aging

The general purpose of the section on aging under Dr. James E. Birren is to identify the primary factors leading to decline in the function and structure of the nervous system with advancing age. This purpose necessitates research to describe the principal age changes which occur in man and other animals and anticipates eventual experiments designed to alter the rate of aging when the primary factors have been identified. Research on the nervous system is one of the most profitable points of departure for studies of aging because of the role of the nervous system in integrating bodily functions and the fact that the nerve cells show little evidence of regeneration, hence it is a system which accumulates changes in time. Senescence of the nervous system is likely one of the major factors in the decline of other organ systems and it is reasonable that research on aging gives emphasis to studies of the nervous system including the environmental factors that operate in the mental health of the individual.

During the year research has been initiated in small animal experimentation with emphasis on changes in speed of conduction in the control and peripheral system. One of the major age changes in behavior of man and other animals is a loss in speed of response.

The first step in the program on the psychophysiology of aging was the description of aging in the peripheral nervous system. Conduction velocity in rat sciatic nerve reaches a maximum at about 300 days of age and shows little change thereafter up to 750 days. The velocity of the "spike" is about 55 m/sec at 37 C. It increases in velocity from about 25 m/sec at 60 days to the normal adult velocity at 300 days. Within the age span of this study no significant decline in conduction velocity was seen in the older rats.

Studies have been initiated on the effects of age on the microscopic appearance of nerve, on conduction velocity in the pyramidal tract of the central nervous system, and on age changes in verbal fluency. Plans are in process of execution for the creation of a colony of aging rats and other small animals among the animal colonies of the National Institutes of Health.

Section Drug Addiction

(Addiction Research Center, USPHS Hospital, Lexington, Ky.)

Throughout the calendar year 1953, the Section on Addicting Drugs under the direction of Drs. Isbell, Wikler, and Fraser, continued investigations concerning the causes, cure and prevention of drug addiction. The human pharmacology and addictive properties of eleven new pain-relieving drugs were studied and reports submitted to the Drug Addiction Committee, National Research Council, who, in turn, forwarded these reports to the Committee of Experts on Drugs Liable to Produce Addiction of the World Health Organization. This group also studied the properties of three morphine antagonists in man. This work was greatly aided by funds made available by the Office of Naval Research, which were allocated to a project designed to discover a synthetic drug which would be a safe substitute for codeine. It is believed that one of the drugs studied, the 3-methyl ether of d-dromoran, may be a substance with the properties desired, provided the results of mass clinical trials substantiate those so far obtained on a limited scale. If this is the case, this is a very important finding since d-3-methyl ether of dromoran can be made synthetically and would obviate the necessity of stockpiling opium in order to assure a supply of codeine in the event of war.

A beginning was made in the important field of endocrinology of addiction. This work may be extremely important since it might lead to an understanding of the physiological mechanisms underlying suppression of sexual drive by opiates, a property believed to be very important in the etiology of addiction. During the first six months of the calendar year, a project on addiction among adolescents was completed. This work showed that adolescent addicts definitely had developed mild physical dependence on heroin. In most cases, adolescent addicts have personality aberrations which may be even more severe than those observed in adults. This project was transferred in July to New York City, where field studies are being conducted under the supervision of the Laboratory of Socio-environmental Studies.

Extensive studies on an extremely interesting drug, N-allylnormorphine, were completed during the year. This agent, though a derivative of morphine, is a specific antidote in poisoning with morphine, methadone, and demerol. It will probably be extremely useful in combating respiratory depression in the newborn. It has already saved a number of lives in cases of poisoning with morphine and similar drugs and is a very useful diagnostic agent in cases suspected of physical dependence on morphine. Even more important is the fact that some of the findings with this substance have caused us to alter previous hypotheses concerning the mechanisms and underlying tolerance and physical dependence and to undertake new experiments designed to test these hypotheses.

Work, which is still in progress, indicates that service symptoms are not likely to follow withdrawal of barbiturates unless the patient has been ingesting at least six or more capsules daily. Studies on the physiological relationships between chronic alcoholic and chronic barbiturate intoxications were begun and evidence, which strongly suggests that these intoxications are in part, at least, physiologically equivalent, was obtained. Studies on chronic alcoholic intoxication were inaugurated and the results, though not yet conclusive, suggest that withdrawal of alcohol from chronically intoxicated persons may cause serious withdrawal symptoms. If this finding is substantiated by further work, it will have considerable influence on the treatment of alcoholics in the future.

Using a special psychological test called the Minnesota Multiphastic Personality inventory, data on the personality characteristics of over 300 adult narcotic addicts were collected. These individuals were found to score high in categories designated "neurotic traits," "psychopathic deviates" and "hypomania." It is hoped that records can be collected on at least 500 addicts, after which correlations will be undertaken in the hope of developing criteria for determining diagnostic and prognostic factors, etc.

Work with N-allylnormorphine was confirmed and extended in experiments on dogs. New hypotheses concerning the genesic of physical dependence were developed. Testing of the hypotheses in dogs is now under way. Following withdrawal of barbital after intoxication for a period of a year, symptoms resembling those seen during abstinence from barbiturates in man occurred in the dogs. This experiment opens the way for initiation of investigations of the chemical and neurophysiological basis of barbiturate addiction.

Section on Endocrinology

(Cooperative Project with the Worcester Foundation for Experimental Biology)

The most important contribution of this project, under Drs. Hudson Hoagland and Gregory Pincus, over the past year has been the development and use of new methods of analysis for urinary and blood steroids of a degree of qualitative specificity and quantitative reliability hitherto unobtainable. These chromatographic methods for the first time permit a delineation on 24 to 48 hour urine samples of patterns of approximately 40 urinary steroids metabolites. The amounts and types of some of these substances appear from preliminary studies to vary with different disease states when they are compared with normal standards for comparable age levels. Since steroid substances play important roles in many diseases the new methods furnish investigative tools of widespread value. So far urinary steroid patterns have been studied primarily in normal subjects but also in a few schizophrenic patients, a few arthritics, and a few cancer cases. The steroid analytical studies have been divided between three of the laboratories, (I) a-ketosteroid study (II) b-ketosteroid study (III) corticoid study.

Another contribution of the project has been the development of improved techniques for determining adrenalin and noradrenalin in urine and blood. This method has been applied to normal persons, schizophrenic patients, arthritic patients, and to animals in relation to stress experiments.

An extensive study of adrenal physiology of normal subjects and schizophrenic patients in the 40-60 year age range has in general confirmed the earlier published findings with normals and schizophrenic patients in the 20-40 year range and has added to our knowledge of differences of adrenal cortical function between the patients and controls both under resting conditions and after experimental stress and ACTH injection.

Finally studies of synaptic conduction in rat brains have indicated that adrenal steroids may play significant roles in the regulation of synaptic conduction.

Laboratory of Socio-environmental Studies

The research program of this laboratory under Dr. John Clausen was initiated during the past 18 months; the bulk of the present staff was recruited and several continuing studies were undertaken.

A project was initiated at St. Elizabeths Hospital to investigate what happens in the family when the male head of a household which includes children is hospitalized for mental illness for the first time. This study is exceedingly broad in scope and is intended as a pilot project to establish the major variables which must be considered in research on factors in family life which influence rehabilitation of the mental patient.

Interviews are being secured with the wives of the patients who meet study specifications as soon as possible after hospitalization. At present coverage is confined to white male first admissions, aged 20-60, who were residents in the District of Columbia or environs with their families at the time of hospitalization and were admitted with diagnoses other than alcoholic or senile. This group will probably total 15 to 20 new cases per year. Certain sub-projects will be developed which will require more extensive sampling in the future. During the first year or two, however, primary attention will be devoted to the sharpening of concepts and the development of schedules and techniques for securing the kinds of data required. This is clearly a core problem for social science research relating to mental health and is one which has been almost wholly neglected by past research.

A field research unit was set up under Dr. Melvin L. Kohn to ascertain the distribution of mental illness in the Hagerstown, Maryland, community and to study the social and spatial mobility patterns of a sample of patients admitted to Maryland mental hospitals from Hagerstown with diagnoses of schizophrenic, manic depressive or involutional psychoses.

The field research station was established shortly after October 1. In the remaining three months of the year most of the basic checking of the names through the files of the Familial Studies Unit has been accomplished and substantial progress has been made toward mapping the areas of the city. The next step will be the selection of comparison groups and the tracing of residential and occupational histories.

The testing of hypotheses with reference to the social and spatial mobility of functional psychotics is clearly a basic step toward more adequate knowledge of the etiology of the functional psychoses. In addition, the mapping of the social areas of Hagerstown and a systematic study of the structure of the community will afford a necessary backdrop for subsequent research in this community. A good deal of the work that will be accomplished during the first year in Hagerstown must be regarded as "tooling-up" for subsequent studies.

Thus far, to our knowledge, there has been no attempt to combine study of the genetic, ecological, and social psychological processes to analyze the distribution of functional psychoses in our society. Such an analysis is a long-range objective of the project undertaken in Hagerstown and Washington County.

In addition, the necessary theoretical formulations have been completed for studies by Dr. Lyman Wynne on relationships between personality and sociocultural systems, and an occupational role-identity in adolescence. Field studies have been initiated by the unit on juvenile drug addiction, and a new project under Dr. Gordon Allen on genetic factors in mental deficiency has been established in collaboration with Dr. Franz Kallman, Head of the Department of Medical Genetics, New York State Psychiatric Institute.

Clinical Psychiatric Research

A project on the objective and quantitative analysis of spontaneous verbal behavior was initiated during 1952 by Dr. Louis Gottschalk and Gove Hambridge, Jr. Verbal productions form the large bulk of auditory cues used by the psychiatrist and clinical psychologist in their work. At the present time, these productions represent by far the larger part of the raw data for investigators and therapists in these fields. Gross summaries stated in an objective, impressionistic, and often enough authoritative manner are common. Because of the difficulties in the systematic organization and presentation of raw data, conclusions frequently go undocumented. The specific aim of this research project is to develop a method of recording, codifying, and analyzing verbal behavior in a predictably reproducible manner.

The past year has been devoted largely to a development and evaluation of recording, measurement and tabulating techniques for the systematic and objective analysis of spontaneous speech with respect to form and content. Preliminary findings suggest an ability to differentiate between patients with and without psychiatric illness on the basis of these objective criteria.

A pilot study has been undertaken with patients provided through cooperation of the Army Medical Center, to investigate the relationships between verbal behavior and cortical electrical activity as recorded by the electroencephalograph.

Studies at Clinical Center

The only member of the clinical research staff appointed thus far is the director. Consequently the proposed research program can be described only tentatively since its final direction will be determined by the specific interests of those who accept staff positions.

It is anticipated that there will be three major areas of interest: the psychoses, psychosomatic reactions, and behavior problems of children. Patients will be studied intensively by the various psychiatric techniques ranging from brief and group psychotherapy to the analytic. Simultaneous correlations will be made with physiological and biochemical observations on the one hand, and socio-psychological studies on the other. Staff attitudes toward the patients will be compared to familial attitudes which might have played some role in the genesis or perpetuation of their pathological reactions. The facilities of the Clinical Center provide unique opportunities for such an integrated approach to the problem of mental illness, and should greatly increase our understanding by making it possible for the clinical physiologist, for example, to take into account variables in the social field which affect his observations.

A unifying interest among the various disciplines will be an interest in a theory of personality development based upon verificable clinical observation. The group interested in this problem will integrate the data discovered in the various projects, and will feed back to the project investigators critical questions for experimental proof.

Within this broad framework it is anticipated that individual contributions may be made in such diverse fields as the relationship between physiological change and behavior, group dynamics, linguistics, psychological testing, communication theory, and many others.

NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

Russell M. Wilder, Director

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NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES

July 1, 1951 - December 31, 1952

Introduction

For the period of this report, the Institute has conducted and supported research on arthritis and rheumatism, various metabolic diseases, and fundamental problems of metabolism. Intramural studies have been done in the four basic science laboratories--Chemistry, Physical Biology, Biochemistry and Nutrition, and Pathology and Pharmacology--which constituted the former National Institute of Experimental Biology and Medicine. Hence, many of the intramural projects were initiated prior to the establishment of the present Institute in 1950. These continue to be highly productive.

A major area of activity has been the development of extramural programs, utilizing funds appropriated for distribution to nonfederal institutions, scientists, and physicians. The purpose of these programs is to foster and support research in arthritis and the metabolic diseases and to increase the number of specially trained workers in these fields.

In addition, the Institute has engaged in recruiting a staff of clinical investigators to man the facilities of the Clinical Center. These scientists, for the most part, are now engaged in research in other institutions pending their transfer to the National Institutes of Health. The planning of projects to be undertaken in the Clinical Center has been a major pursuit during the year.

LABORATORY RESEARCH

Floyd S. Daft, Assistant Director, is Chief of Laboratory Research. Broad attack on the problems of metabolism, which are vitally important to the understanding of arthritis and metabolic diseases, has been continued.

Investigations have continued on the relation between the nervous system and the endocrine glands--particularly the pituitary and adrenals, which appear to be involved in the collagen diseases. Further progress has been made in the search for plant materials from which cortisone and other steroidal hormones might be manufactured, and in the synthesis of those hormones from simpler compounds. Methods have been devised or improved for the determination of adrenal hormones in tissues and body fluids, including a new method for measuring minute amounts of cortisone.

A technique devised during the past year permits the quantitative estimation of very small amounts of insulin in blood. This makes possible an attack on many problems in the field of diabetes which previously could not be studied successfully.

It has been shown that histidine may be metabolized through urocanic acid to glutamic acid and that rats deficient in the vitamin folic acid fail to carry this degradation to completion. This gives a metabolic test for folic acid deficiency in animals and possibly in man. The citrovorum factor, related to folic acid, has been isolated and its structure determined. Studies are in progress to determine the forms in which these important vitamins function within the body.

In an effort to develop replacements for morphine and its derivatives, new analgesics have been synthesized and tested. Some show considerable promise of replacing morphine and codeine. Identification tests for the new compounds have been devised which will be of value in police and control work.

The hemorrhagic condition that follows radiation injury has been prevented in animals by repeated platelet transfusions. Progress has also been made in preventing post-radiation infection and death by means of antibiotics and spleen homogenates. New observations bear on the effects of large doses of radiation upon the central nervous system, and there are indications that a circulating toxic substance is present in the body under these conditions.

"Factor 3," a substance that prevents dietary liver necrosis in rats, has been partially purified. Evidence has been obtained for the presence in casein of a new factor that affords protection against the development of fatty livers. It has also been shown that certain amino acids, plus antibiotics, improve greatly the nutritive value of rice diets, and that antibiotics or large amounts of vitamin C permit rats to grow almost normally without dietary sources of many of the B vitamins.

The results of studies on shock, indicating the value of orally administered salt solutions, are discussed in a previous annual report. The value of salt in the prevention of shock from burns is now under clinical trial. Recent animal studies have shown that massive doses of sulfonamides or antibiotics are of value in preventing late deaths from burns.

These and other important results are discussed in more detail in the following sections.

Laboratory of Physical Biology

The Laboratory of Physical Biology (Heinz Specht, Chief) has as its general objective the study of the physical aspects of living material, from the point of view of structure and function as well as the physical stresses of the environment which influence them. Because these viewpoints are quite diverse, the various studies in this Laboratory are also diverse, forming a multiple attack on basic problems in this field. This type of approach has been fruitful, partly through the many opportunities for leads, and partly through the exchange of ideas and cooperation between investigators in the different disciplines.

Section on Molecular Biophysics

Ralph W. G. Wyckoff is chief of this section. The visualization of the macromolecules of living matter was continued, using the electron microscope with the aid of the thin sectioning technique. Some of the electron microscopic investigations carried out were on rabies inclusion bodies, vaccinia virus in chick embryo membranes, PR-8 influenza virus in chick embryo membrane, Newcastle disease in chick embryo membrane, Rous sarcoma in chick embryo, the structure of pollen membranes, polyhedral virus diseases affecting the larvae of the privet hawk moth, the structure of hyacinth root cells, cell divisions in onion root tip cells, reprecipitated collagen, structure and development of the cell wall in Valoniaceae and developing bacteriophage with particular reference to possible immature forms. (Wyckoff.)

More was learned through the use of radiophosphorus about the metabolic changes occurring in normal and X-ray irradiated bacteria diseased with bacteriophages and about the source of the nucleoprotein phosphorus of the mature bacteriophages. It was found that the phosphorus anabolism of X-ray irradiated bacteria is stimulated by the infection with bacteriophage in a manner similar to that occurring in ultraviolet irradiated organisms. It was also found that all seven of the T series bacteriophages active against E. coli take the same amount of phosphorus per particle from the host, but that this same amount of phosphorus can come from different host compounds as a function of the infecting bacteriophage. (Labaw.)

Subsection on Physical Biochemistry

The systematic investigation of membranes and membrane model systems of biological interest was continued in particular work on permselective membranes--that is, membranes of highest ionic selectivity. (Sollner, Neihof, Dray, and Tamamushi.)

In particular, the methods of preparation of strong acid-type membranes were perfected in detail, and accurate measurements of their electromotive action in concentration chains were started. (Sollner and Neihof.)

Data on the resistance of electropositive (anion permeable) and negative (cation permeable) permselective membranes were evaluated and published, and the close correlation of the physical chemistry of membranes and of ion exchangers was pointed out. (Sollner.)

The systematic study of the bi-ionic potential (BIP) was continued. An explicit theory was developed for the calculation of the potentials arising in degrading BIP systems, the calculations being based on the previously developed theory of the bi-ionic potential in undegraded systems. A theoretical investigation of the electrochemistry of polyionic membrane chains was started in preparation of an experimental attack on this problem. These studies begin to crystallize into a rational physicochemical basis of electrophysiology. (Sollner and Dray.)

A systematic study was started of Donnan membrane equilibria in selected systems which are accessible to an accurate physicochemical treatment. (Sollner and Tamamushi.)

Section on Low Energy Radiation Biology

Frederick S. Brackett is chief of this section. Continuing our studies of photosynthesis, new experiments have been initiated (Brackett, Olson, and Crickard) to determine the absolute magnitude of quantum efficiency in monochromatic light of any wave length and known purity. Apparatus has been designed, built, and perfected which provides continuous simultaneous recording of both oxygen concentration and the integrated value of diffusely transmitted radiation. Provision has been incorporated for restandardization of measurements.

Results of our previous study on photosynthesis, providing knowledge of time course and intensity dependence, have been presented in invited addresses both at the University of Chicago and at a symposium in Gatlinburg, Tennessee, sponsored by the National Research Council and the Atomic Energy Commission. Two papers are in process of publication.

Preparations are nearly completed for a study of the photochemical production of tachysterol from ergosterol in monochromatic ultraviolet, through analysis of ultraviolet and infrared spectra. (Brackett and Rowe.) Tachysterol is of health importance because of its relationship to vitamin D in nutrition and its occurrence in vitamin preparations.

Advances have been made in the technology of spectral recording through the development of a successful error-signal control of recording rate, as well as automatic adjustment of sensitivity and time constant for changing demand in logarithmic recording of transmission. (Daniel and Showkeir.)

Cooperative work with Olson and Mattern of the National Microbiological Institute on light scattering by cells and its application to blood count and bacterial research is continuing.

Appraisal of the haemoscope (an instrument for red blood cell counting by scatter photometry, with an adaptation for hemoglobin determination) has been completed, and a report has been submitted for publication.

Section on Nuclear Radiation Biology

Howard L. Andrews is chief of this section. The work done under contract with the Armed Forces Special Weapons Project in connection with Weapons Test Jangle has been completed. The report of work directed by personnel of this section is in six volumes, two of which are essentially projects carried out by section members. This work has added considerable basic information on both offensive use of and defensive measures against atomic weapons. (Andrews, Smith, and Maxwell.)

Studies on the mechanism of action of antibiotics in radiation injury suggest strongly that the action of spleen implants in reducing mortality is primarily an increased resistance to infection through a stimulated production of white blood cells. (Smith.)

Evidences of radiation injury in simple animals (hydra) have been found to be greatly reduced by increasing the concentration of magnesium ions in their environment following irradiation. Although hydra are a long way from man, this is an important lead, since it is one of the few treatments known that is effective when given after the radiation has been received. (Daniel and Park.)

Studies on the effects of radiation on spleen have shown a marked decrease in the ability of this organ to maintain or synthesize high-energy phosphorus compounds. The exact mechanism of this effect is being studied to determine more completely the role of spleen implants in radiation protection. (Ashwell and Maxwell.)

Work on radiation effects in large molecules such as proteins has been continuing in an attempt to determine why some polymerize while others split into smaller fragments, but no definite conclusions can be drawn at present. (Carroll.)

The studies of the products formed from amino acids by radiation have proved to be more complex than was first thought because of the effects of oxygen on the reactions. This is in line with the observation that radiation mortality can be reduced by prior administration of reducing substances. (Maxwell and Sharpless.)

Studies of ionization at high altitudes due to cosmic rays have continued, and several heavy ions have been identified in special photographic emulsions. (Yagoda.)

Studies on the effects of large radiation doses with particular reference to the central nervous system suggest strongly that at least part of radiation injury is due to a circulating toxic substance rather than a direct action of radiation on tissue. If this is confirmed, the chance of successful treatment of radiation injury will be greatly improved. (Andrews and Brace.)

A very satisfactory method of radioactive waste disposal has been worked out and is now in routine use through the cooperation of the U. S. Coast Guard. (Andrews and Archer.)

Replacement therapy by forcing phosphorus intake appears practical in the event radioactive phosphorous accidentally enters the body. (Archer and Cool.)

Section on Physiological Physics.

Heinz Specht is chief of this section. The study of the effects of low oxygen pressures has been continued along several lines. High-altitude acclimatization in rats (Altland) has been investigated as regards the effect on the life cycle, particularly the longevity of chronic intermittently exposed animals. Intensive studies on the effects of high-altitude exposure on the reproductive system of male rats, particularly on the history of primordial and definitive germ cells, have been carried out. An investigation of its effect on the hemopoietic system of rats in conjunction with folic acid antagonists and on poikilotherms such as the turtle was also carried on. A study of high-altitude-stress-evoked endocarditis was made (Altland and Highman), with particular reference to the use of such animal preparations for the investigation of bacterial infections and their treatment with antibiotics. The relation of high-altitude exposure and the induced reticulocytosis and polycythemia to effects of radiation sickness were also studied. Circulatory dynamics in dogs have been studied (Marshall) by observing the effect on renal function of high blood viscosity during polycythemia evoked by high-altitude exposures. Observations on blood changes during massive infusions of the highly viscous polysaccharide, Dextra, have demonstrated that erythrocyte dilution is possible without significant reductions in blood viscosity.

Studies on the effects of atmospheric pressure on pulmonary ventilation have been continued (Specht). An index of pulmonary ventilation was devised by observing the rate of nitrogen accumulation in the lungs of subjects who had been cleared of nitrogen before test. The index was applied to the comparison of different methods of manual artificial resuscitation.

Studies in physical biochemistry have been extended in three directions. The analysis of the clotting mechanism of fibrinogen (Laki and Kominz) has been carried out by means of amino acid analysis of the reaction products. Such an analysis of actin, myosin A, tropomyosin, meromyosin L and H (Laki and Kominz) has indicated further interrelations which clarify the problem of the structure of contractile proteins. A similar analysis of myosin and its products after aging (Spicer) relates loss of contractile function to the splitting off of a low molecular weight substance containing pentose. A study of the complexing ability of ATP and cations with actomyosin (Bowen) and on the kinetics of the formation of ADP by muscle phosphomutase is currently under way.

A study of the dependence of cellular metabolism on the partial pressure of oxygen in normal, ligated, and DDT-poisoned fly larvae has been carried on, indicating that various tissues are competing on an equal footing for oxygen, and that there is no special ability of some one tissue to pre-empt the available supply. A study of oxygen transfer across membranes and tissue interfaces is being followed to discover basic relationships in gas and fluid balances between organism and environment.

LABORATORY OF CHEMISTRY

The researches of the Laboratory (Lyndon F. Small, Chief) fall into three major divisions: steroids, carbohydrates, and analgesics. Supplementing these is the analytical laboratory, grouped for convenience with the analgesics section. A report from the chairman of the NIAMD Editorial Committee also follows.

Section on Steroids (Erich Mosettig, Chief)

Structural Elucidation and Partial Synthesis. Plant Sources: steroidal alkaloids (Sato, Latham, and Miller).--In efforts to correlate the structures of tomatidine and solasodine, extensive degradation experiments on both steroidal alkaloids have been conducted. There is nearly complete evidence that 5,6-dihydrosolasodine is not identical with tomatidine. These studies, moreover, showed that the structural formula proposed by Briggs (New Zealand) is most likely erroneous. For securing the glycoside solasonine, 27 lbs. of air-dried seeds of Solanum xanthocarpum (from India) and 10 lbs. each of Solanum sodomaeum and Solanum marginatum (New Zealand) were extracted and processed for solanine and solasodine.

With the aim of elucidating the structure of veratramine, and correlating it with that of Jervine, veratramine has been degraded by a series of reactions (incl. Hofmann and Emde) to N-dimethyldesoxyhexahydroveratramine (the nitrogen ring opened), and finally to nitrogen-free products.

Plant sources: steroidal sapogenins (Scheer and Kostic).--Because of their practical importance as potential industrial source material for the partial synthesis of cortisone and allied compounds, a series of steroidal sapogenins (A/B allo and normal, ring F, a and b configuration) were studied in respect to stereochemical relation of the corresponding dihydro-genins and dihydro-pseudogenins. The significance of these dihydrogenins lies in their oxidability to a number of pregnene derivatives (starting material for progesterone, androgens, and corticoids); secondly their structures are intimately related to the analogous "side chains" of tomatidine and solasodine.

Plant sources: ergosterol (Nes and Kostic).--As an approach to the synthesis of cortisone from ergosterol, $\Delta^{7,9(11),22}$- ergostatrienol and its acetate were hydrogenated in order to determine the possibility of obtaining derivatives with an isolated $\Delta^{9(11)}$- or $\Delta^{8(9)}$- double bond for the introduction of an 11-oxygen function. Platinum oxide and Raney nickel give largely the Δ^{7}-compound; copper chromium oxide under mild conditions, $\Delta^{7,22}$-ergostadienol, $\Delta^{8(14)22}$-ergostadienol, $\Delta^{8\ (14)}$-ergostenol, and one or more C3-OH epimers--the ratio depending upon time and temperature. Finally, $\Delta^{8(14),22}$-ergostadienol could be obtained by the catalyst-induced isomerization of $\Delta^{7,22}$-ergostadienol in a yield of 54 percent.

Other studies of oxygen introduction at C-11, through addition of various agents to $\Delta^{5,7,9(11),22}$-ergostatetraenyl acetate, led to the discovery of a novel skeleton rearrangement under the influence of hydrogen chloride. Evidence accumulated thus far points to the structure of an s-octahydroanthracene for the chief rearrangement product.

Total synthesis towards cortisone (Fry and Miller).--Synthetic routes to hydrogenated phenanthrenes (with an oxygen function in the position corresponding to C-11 in the steroidal skeleton) are being explored, utilizing a 2,5-dihydroxycyclohexylacetic acid as starting material. From this compound two of the principal building components, the necessary cyclohexenone derivative and a cyclohexane ethanol, can be constructed, which may be condensed to give an immediate precursor to cortisone and closely allied (e.g., nor derivatives) 11-oxygenated corticoid-like substances not found in nature.

Analytical and metabolic studies (Heftmann, Hayden, Berner and Miller).--For the analysis of cardio-active glycosides, the corresponding aglycones, and their acetates, a paper-chromatographic method has been developed. Seed extracts (up to 0.5 mg.) were prepared from some 70 samples of various Strophanthus and (only partially identical) Apocynaceae species (plant material supplied by the Plant Industry Sta., Beltsville, Md., Dept. Agric.) chromatographed and rechromatographed after acetylation and after subsequent hydrolysis. A number of seeds were found to contain sarmentogenin and several other known cardiac aglycones. Several seed samples contain unknown glycosides and aglycones. Similarly, a chromatographic procedure for the identification of steroidal sapogenins and their acetates was developed. In that method the spots were made visible by spraying the paper with either blood or trichloroacetic acid.

For the quantitative recovery of urinary corticosteroids, a continuous solvent-extraction has been devised which permits simultaneous hydrolysis and extraction. The extractor operating under vacuum can be used at room temperature with relatively high-boiling solvents, without undue exposure of the liberated corticoids to heat or acid.

Two technicians of the Endocrinology Branch, National Cancer Institute, are performing routine analyses on the urinary steroids excreted by cancer patients undergoing hormone therapy. This work, which is directed by the head of this unit, involves analyses of 17-ketosteroids, corticosteroids, and pregnanediol. The methods are evaluated by duplicate and recovery experiments and various refinements--e.g., fractionation of a- and B-hydroxy-17-ketosteroids. Elimination of interfering chromogens is employed as needed.

Section on Carbohydrates

H. G. Fletcher, Jr., is chief of this section. A program of research on methods for the synthesis of carbohydrates and carbohydrate derivatives has been continued.

One of the most valuable methods for the synthesis of ketoses is the microbiological oxidation of sugar alcohols by Acetobacter suboxydans, an organism which is used for this purpose at one step in the synthesis of vitamin C. Unfortunately the organism is most selective in its action, converting some sugar alcohols to the corresponding 2-keto sugars and leaving other sugar alcohols unattacked. One facet of the program of the section entails study of this specificity with the object of formulating, if possible, a generalization relating the configuration of a sugar alcohol with its fate in cultures of A. suboxydans. In the course of this work, it was found that the w-deoxy sugar alcohol L-fucitol is oxidized by the organism to a 4-keto sugar, an unexpected and novel type of sugar in sharp contrast to the known ketoses which are all 2-ketoses. (Richtmyer and Stewart.)

During the past eighteen months, a variety of w-deoxy sugar alcohols have been synthesized and some have already been subjected to the action of A. suboxydans. Work along this line is continuing with the aforesaid objective of evolving a generalization regarding the mode of action of this useful organism. (Zissis.)

While the above work deals primarily with the biochemical synthesis of sugars, a second phase of the program of the section is concerned with purely chemical methods of synthesis. The enhanced stability of the benzoic acid derivatives of the sugars compared with other acyl derivatives strongly suggests the utility of these derivatives in the synthesis of a variety of relatively labile derivatives of the sugars which are of biological significance: O-glycosides, nucleosides, vitamin B_{12}, etc. Previous to the period of this report, a study of the benzoyl derivatives of the sugars had led to the evolution of a new method for the synthesis of aldopyranosides. Recently this work has been extended to other aldopyranosides and also to a ketopyranoside. With this background, attention has been directed to the synthesis of aldofuranose derivatives, and a process for the preparation of the two isomeric D-xylofuranose tetrabenzoates has been developed. The program has now progressed to an attack upon the problem of the synthesis of ribofuranose derivatives, since ribose occurs in biological systems largely if not wholly in the furanose form. (Fletcher, Ness and Diehl.)

It has been known for many years that some monosaccharides are readily converted with warm aqueous acid into anhydrides (called glycosans), while other sugars are not affected. The structure of these anhydrides and the relationship between the structure of sugars and the ease of their conversion to glycosans have been objects of investigation in this section. The anhydrides from D-altroheptulose, L-guloheptulose, and D-idoheptulose have now been shown to be all 2,7-anhydro-B-heptulopyranoses. An anhydride obtained from D-gluco-D-gulo-heptose has been shown to be a 1,7-anhydro-B-heptopyranose, while evidence has been obtained that the sugars D-gluco-D-ido-heptose and D-gulose both give anhydrides of the 1,6-anhydro-pyranose type. The work on glycosans carried out in this section has provided the means whereby groups in other laboratories have been enabled to identify D-altroheptulose (sedoheptulose) as an intermediate in photosynthesis and also in one enzymic path of the breakdown of D-glucose. (Pratt.)

As part of the work of the section, newly available chemical agents are regularly examined for their possible utility in carbo-hydrate synthesis. In the last report period, lithium aluminum hydride was shown to be valuable for the synthesis of the 1,5-anhydro-glycitols such as styracitol. More recently the value of this reagent in sugar chemistry has been explored through the reduction of various sugar acids, an acetohalogenoaldofuranose and tetrabenzoyl-B-D-fructofuranosyl bromide. The latter case, incidentally, offered the first opportunity for studying the stereochemistry of the replacement of a tertiary halogen by hydrogen. (Fletcher, Ness and Diehl.)

This section has long been concerned with improvements in the methods for the preparation of rare sugars so that these substances may be more readily available for biological and medical experimentation. In the course of the past eighteen months, improvements were published for the preparation of L-xylose, melibiose, styracitol, L-arabinose, and L-glucose. (Fletcher and Diehl.)

Among important byproducts of the above research activities may be mentioned new data on the identification of the sugars through the benzimidazoles of the sugar acids.

Section on Analgesics

The over-all objective of the section (Nathan B. Eddy, Chief) is collaborative effort, chemical and pharmacological, in the preparation and evaluation of new substances, potentially analgesic, leading to elucidation of the relation of chemical structure to action and to possible clinical applications. A major function of the section is consultative, carried out mainly by the chief of the section, in the field of analgesics and narcotics generally, for other government agencies, for the National Research Council, for pharmaceutical manufacturers in this field, for the World Health Organization, and for the National and International organizations for narcotics control.

Chemical Laboratories. Derivatives of isomethadone (May).--Reduction of the keto group of *dl* isomethadone and its optical isomers with lithium aluminum hydride produced only one of the two possible diastereoisomeric alcohols (designated a-*dl*, a-*l*, and a-*d*-isomethadols) in excellent yield. When reduction was effected with sodium in propanol, the other possible diastereoisomer (B-form) resulted predominantly, although appreciable amounts of the a-isomers were also obtained. Each of alcohols was acylated with acetic anhydride-pyridine (acetylderivatives).

Experiments in the methadone series (May and Perrine).--An attempt to methylate a-*dl*-methadol [$(CH_3)_2$ NCH $(CH_3)_2CH_2CPH_2$ $CHOHC_2H_5$] sulfate with dimethyl sulfate in boiling ethyl acetate gave, instead of the O-methyl derivative, an alcohol isomeric with a-*dl*-methadol. The isomeric alcohol was proved to be 6-dimethylamino-3,4-diphenyl-4-heptanol, by a Hofmann degradation and hydrogenation of the resultant non-nitrogenous olefin to 3,4-diphenyl-4-heptanol, identical with that synthesized from a-ethyldesoxybenzoin and propyllithium. A by-product of the reaction which formed the isomeric alcohol was a desoxy compound, whose ultraviolet absorption spectrum, chemical properties and analytical data were compatible with those of a-ethyl-a'-(2-dimethylaminopropyl)stilbene. The isomeric alcohol had only very weak analgesic action, indicating that asymmetry in the position of the phenyl rings is a disadvantageous modification of the methadone structure.

The reaction of methanesulfonyl or p-toluene-sulfonyl chloride and a-*dl*-methadol led to the methochloride of a desoxymethadol as the only isolable material. This was proved to be either 1,5-dimethyl-3,3-diphenyl-2ethyl-pyrollidine or 1,2,6-trimethyl-4,4-diphenylpiperidine by Hofmann degradation to a product still containing a basic nitrogen. Hydrogenation of the Hofmann degradation product gave 6-dimethylamino-4,4-diphenylheptane or an isomer thereof. An attempt is being made to synthesize this product for final proof.

Synthesis of potential analgesics from 2-phenylcyclohexanone (May and Murphy).--This readily available starting material can be converted to simple nitrogenous compounds having several structural features in common with such potent analgesics as morphine, dromoran, methadone, and demerol. Alkylation of the ketone gave 2-(2-dimethylaminoethyl)-2-phenylcyclohexanone whose C-O group was reduced to CH_2 and to CHOH. Acetylation of the latter was also effected. Cyclization of the aminoketone led to a phenylmorphan in which the nitrogen is heterocyclic as in morphine and demerol. The attempt to convert the phenylmorphan derivative to a hydrophenanthrene isomer is proceeding satisfactorily. The phenylcyclohexanone derivatives so far tested have not shown analgesic action. They are, however, only early steps in the intended build-up on the basic molecule.

The O-acetyl derivative of d-dromoran was prepared and showed distinct morphine-like effects in mice and cats, although the d-dromoran itself is inactive.

The study of demethylation of amines with potassium ferricyanide is continuing. (Perrine.)

The study of the reactions of 9-vinyl-acridine is continuing. (Perrine.)

Wolfe-Kishner reduction and mercaptol deoxygenation of dihydrocodeinone was completed. One product, ethylmercaptodihydrothebainone, showed moderate analgesic effect about half that of codeine but only one-fourth that of dihydrothebainone. (Perrine.)

A program has been undertaken to utilize 2,2-diphenyl-4-dimethylaminovaleronitrile in the synthesis of potential analgesic agents, beginning with reduction to the corresponding aldehyde (a known reaction which we have developed to give rapid and very satisfactory conversion) and subsequent substitution of the nitrile (or aldehyde) part of the molecule by mercapto, sulfonyl, keto, pyrimidyl, etc., groups. (Perrine.)

Work has continued throughout the period on the elucidation of structure of the morphine derivative, metopon. Effort has been directed toward synthesis of 3,4,5-triethyl-5,6-dimethoxytetrahydronaphthalene, the novel degradation product derived from dihydrothebaine. Two approaches to this synthesis have failed along the way; two new approaches remain to be undertaken. (Sargent.)

Aminoacridines have been reported recently to antagonize some of the effects of morphine. To test this action with respect to analgesic effect, 9-aminoacridine and 1,2,3,4-tetrahydro-9-aminoacridine were synthesized. Neither was antagonistic to the analgesic effect of morphine in mice; the latter was convulsant and very toxic. (Sargent.)

To elucidate the structure of several new acridine antimalarials (first prepared in this laboratory), the synthesis of the four unknown ethylacridines was undertaken. Three have been prepared and the fourth is well under way. (Sargent.)

A new and simple method has been devised for the preparation of the powerful analgesic dehydrodesoxymorphine-D ("Desomorphine"). This consists in conversion of dihydrocodeine to its tosyl ester, reduction with lithium aluminum hydride, and subsequent demethylation. (Small.)

A number of new types of morphine derivatives has been prepared for analgesic testing, by introduction of hydroxyl groups with osmic acid into such narcotics as morphine, heroin, and neopine. (Small.)

For police and control purposes, specific identification tests were developed for the new synthetic drugs demerol, nisentil, methadone, and dromoran. The tests will distinguish these drugs from each other, from the narcotics of the opium and coca group, and from various medicinals not controlled by Federal law. (Small.)

In connection with determination of the configuration of the basic portion of the cocaine molecule, a study of the stereochemistry of the related bases tropine and pseudotropine has been carried out. The most important result of this has been isolation of two isomeric N-substituted tropines which owe their isomerism to a pseudoasymmetric nitrogen atom, a hitherto unreported phenomenon. (Findlay.)

Research on new analytical methods has resulted in a Dumas nitrogen procedure which is applicable to organic compounds heretofore resisting all analytical methods. In service capacity, 14,200 analytical determinations were made. This includes over 1700 lactic acid analyses by Mr. Remsburg for a continuing project of the National Microbiological Institute. (Alford.)

Studies on the catabolism of amino acids center around the twofold oxidation of tryptophan and tyrosine. By exchange of iodo groups with hydroxyl, three new hydroxyhistidines have been prepared. Application of a similar method to imidazolepropionic acid is expected to be useful in identification of the labile isomer of formylisoglutamine isolated, by Silverman, Tabor, and associates, from folic acid deficient animals. Synthesis of possible metabolites of hydroxyproline, by controlled oxidation of suitable derivatives, and from urocanic acid, is in progress. (Witkop and Beiler.)

Pharmacological Laboratories (Eddy and Leimbach). Evaluation of many compounds for analgesic and toxic effects was completed, using the assay method devised in this laboratory. These included dithienylbutenyl- and dithienylbutylamines, a large number of methadone derivatives (mainly alcohols and acylated alcohols derived from methadone, isomethadone. and their optical isomers), new morphine derivatives, phenylcyclohexanone derivatives, and a number of other diphenyl compounds. The unsaturated dithienyl compounds were more effective than the saturated, and, in some instances, exhibited analgesic activity approximating that of morphine. All of the dithienyls showed remarkably weak analgesic effect when administered orally and a very much wider difference in analgesic effectiveness than in toxicity with oral and subcutaneous administration. Among morphine derivatives the difference in effectiveness by the two routes of administration is not at all uniform. In some instances the oral dose is 100 times the subcutaneous, in other cases only about twice as great. Comparisons in the morphine series is being extended to see if the differences can be related to any chemical configuration.

The alcohols derived from the methadones and isomethadones, with one exception, were much weaker analgesics than the ketones; the acetylated compounds, on the other hand, were all more effective than the parent ketone. The alcohols and acetylated alcohols derived from d-methadone were as effective or more effective orally than subcutaneously and were relatively long acting. This was not true of the compounds derived from d-isomethadone. Throughout, isomethadone and its derivatives are less toxic and less analgesic than corresponding members of the methadone series.

Work along three lines having to do with the general phenomena of analgesia is under way: (a) acute tolerance to analgesic effect, (b) the ability of various agents to antagonize or potentiate the effect of different types of potent analgesics, (c) variation in analgesic effect with season and different lots of mice.

In collaboration with Drs. Brodie and Axelrod of the National Heart Institute, a beginning was made on metabolic studies designed to throw light upon differences in effect with route of administration and upon differences in speed and degree of effectiveness in different species.

The Survey of Chemotherapeutic Agents (Hunter). The Survey Office of Chemotherapeutic Agents serves primarily as liaison between the Chemical-Biological Coordination Center of the National Research Council and various laboratories of the National Institutes of Health. From July 1951 through December 1952, 1,556 compounds were processed. These were obtained primarily from the Chemical-Biological Coordination Center, further from laboratories of the National Institutes of Health, academic and industrial laboratories, and from miscellaneous private sources. Laboratories of the National Institutes of Health cooperated in the testing for toxicity, analgesia effect, tumor-necrotising effect, experimental malaria, schistosomiasis, and fumicidal, insect, and snail control. The results of 742 tests were communicated to this office.

NIAMD Editorial Committee (Charles I. Wright, Chairman). The Editorial Board of NIAMD, a scientific-administrative service attached to the Laboratory of Chemistry, received and recorded 373 manuscripts (ranging from books to abstracts) since July 1951. Each manuscript was usually assigned to two or more members of the Board, including the chairman, for review. When no board member qualified, the chairman sought and received aid from members of the other Institutes or occasionally from persons in the National Bureau of Standards, Carnegie Institution of Washington, or Naval Hospital Research Laboratories. The evaluation of each reviewer's comments was made by the chairman, especially when a manuscript was not recommended for publication or severely criticized. Such a manuscript required consultation with the author and a second or third reading before final approval or rejection.

LABORATORY OF BIOCHEMISTRY AND NUTRITION

The Laboratory of Biochemistry and Nutrition (James M. Hundley, Chief) is organized to conduct both fundamental and applied research in the broad fields of biochemistry and physiology. Within the Laboratory, the Section on Fractionation and Isolation searches for and isolates chemical substances from natural sources such as vitamins, growth factors, or other substances of biological importance. The Section on Enzymes studies the fundamental chemical processes by which an organism derives energy from its food, and isolates and studies the enzymes and substrates involved. The Section on Endocrinology studies the influence of the endocrine glands on metabolic processes and various disease states, as well as the interrelations between the central nervous system and the activity of the endocrine glands. The Section on Biochemistry and Physiology of Nutrition studies the actions, uses, and biochemistry of vitamins and amino acids and the role of nutrition in various disease processes, and searches for new vitamins and other substances of possible medicinal importance. Studies are being made on the growth, development, and nutritional status of human beings. The overall program of the laboratory is planned to emphasize research bearing on arthritis and allied diseases, peptic ulcer, and diseases of the liver and blood-forming organs.

Section on Biochemistry and Physiology of Nutrition (James M. Hundley, Chief)

Nutritional Requirements. A nutritionally complete purified diet for the guinea pig has been developed which will maintain normal growth and physiological functioning. With this diet, deficiencies of pantothenic acid, choline, folic acid, niacin, pyridoxine, thiamine, and riboflavin have been produced in the guinea pig. A purified diet has been developed which permits young rabbits to grow as well as on a commercial feed. The rabbit, like the guinea pig, requires a fairly high level of potassium in its diet. The rabbit appears to be the only non-ruminant studied that requires no dietary source of thiamine or riboflavin. Investigations are under way on the still unidentified vitamins that are required by the chick. The presence of such substances in natural foods has been confirmed, and improved methods of assay therefore have been developed. A vitamin B_{12} deficiency can be produced in chicks fed purified diets that are high in fat, protein, or fiber and by the use of low sulfur diets. When the citrovorum factor is fed to chicks, it is not as active for growth as pteroyl-glutamic acid, but it ~~is~~ as active when injected. (Briggs, Reid, and Wooley.)

The Interrelation of Various Dietary and Physiological Factors. Previous work in this laboratory showed that a diet consisting of rice, salts, and vitamins can be improved by the addition of lysine and threonine. When very low levels of certain antibiotics are added to this diet, rats grow as well as they do on a 15 percent casein diet. The rice diet contains only 6.5 percent protein. The addition of small amounts of aureomycin to a purified diet containing minimal amounts of folic acid increases the chick's requirement for that vitamin. This is in contrast to the folic-acid sparing effect of aureomycin seen under these circumstances in the rat. (Briggs and Pecora.)

Previous work from this laboratory showed that large amounts of vitamin C or a variety of antibiotics prevented the development of deficiency signs and permitted almost normal growth in rats deprived of certain of the B vitamins. Present studies are aimed at elucidating the mode of action of these vitamin-sparing agents. A cooperative project with germ-free animals is under way with the Laboratory of Biology at the University of Notre Dame, to determine whether the bacteria in the gastro-intestinal tract are responsible for the phenomenon. (Daft and Hawk.)

The anemia indicative of a folic acid deficiency occurring in rats fed high levels of iron can be partially overcome by the addition to the diet of large amounts of vitamin C. The degree and incidence of the deficiency depends on the protein content of the diet, the level of iron fed, and the amount of copper present in the diet. (McDaniel.)

Studies in dogs show that 3-acetyl-pyridine, a compound similar in structure to niacin, may under certain conditions replace niacin and under other conditions may interfere with the utilization of niacin. This explains certain anomalous results previously published by other laboratories. (McDaniel.)

The leukopenia and granulocytopenia developing in rats fed a diet containing "sulfasuxidine" could be partially overcome by the addition of adenine or thymine to the diet. These and other findings indicate that folic acid deficient rats are unable to synthesize sufficient adenine for white cell formation. (Daft.)

A cooperative study with the University of Wisconsin has shown that in rats raised on a diet low in labile methyl groups, vitamin B_{12} was able to replace choline, as shown by growth and prevention of hemorrhagic kidneys. Choline is more effective than vitamin B_{12}, in maintaining normal levels of fat in the liver. Methionine will not completely replace choline even in the presence of supplementary vitamin B12. (Hawk.)

The Relation of Diet to Physiological and Biochemical Functions. Dietary liver necrosis is fundamentally different from fatty infiltration and cirrhosis. Work in this unit has shown that the methyl group donors (with the exception of methionine) and the vitamins involved in methyl group metabolism (citrovorum factor, folic acid, and vitamin B_{12}) enhance the development of liver necrosis. All of these substances prevent or ameliorate fatty infiltration of the liver and cirrhosis. (Schwarz.)

Starting with a casein digest, a method has been developed for the preparation of a highly purified concentrate of Factor 3, which is a substance that prevents dietary necrotic liver degeneration (cystine and vitamin E are also active). (Schwarz.)

Rats that have been kept for more than 3 or 4 weeks on diets producing dietary liver necrosis show a marked increase in the concentration of liver citric acid after the injection of sodium fluoracetate. They also show a deficiency in their ability to detoxify bromobenzene. The biochemical defect occurs long before death from necrosis. The LD_{50} was 1/20th to 1/30th that of the normal controls. Both vitamin E and Factor 3 brought the tolerance for bromobenzene back to normal. (Schwarz.)

During the preparation of Factor-3 concentrates from enzymatic casein digests, evidence was found for the presence of a new substance involved in methyl group metabolism. The substance affords protection against experimental fatty livers. These findings may be related to the observation that skim-milk powder has been found to be the most effective treatment for human fatty livers and cirrhosis due to malnutrition (kwaskiorkor). (Schwarz.)

Other work in this unit has shown that the livers from rats raised on a choline-free diet containing 10 percent casein were considerably lower in citrovorum factor and in total folic acid activity than livers from choline-supplemented animals or those raised on a 20 percent casein diet. The effect of choline on the citrovorum factor content of the liver was not related to growth rate or to food intake. There was an inverse relation between the degree of fatty infiltration of the liver and the concentration of folic acid and citrovorum factor. Methionine was more effective than choline in restoring the liver to normal. (Schwarz.)

A study of experimental obesity in animals has been started. An attempt is being made to determine the physiological and biochemical effects of obesity produced by purely dietary means. For this work, a technique has been developed for analyzing the entire carcass of laboratory animals. Analyses of rats whose body-fat content ranges from 3 to 30 percent showed that the protein percentage is very constant in spite of the wide range of fat levels. This finding implies that as the animal gets heavier due to the deposition of fat, its muscle mass increases,in proportion to the extra load that has to be moved about. In this work, rats have been raised from weaning on a diet providing 80 percent of the calories from fat. These animals have grown as well or better than those on stock diets and have shown no signs of ketosis. It has always been assumed that a diet in which more than 50 percent of the calories came from fat was deleterious in a number of respects. (Mickelsen.)

When thyroidectomy was performed on new-born rats, the animals grew poorly and showed a low level of myosin and other proteins in their muscles. The injection of growth hormone to these animals resulted in a marked gain in body weight, but with a markedly retarded gain in muscle weight and no increase in the concentration of myosin. When a dog was thyroidectomized at birth, the muscles never developed the dark red color of the normal animal. These studies show that the thyroid hormone may play an important role in the development and composition of skeletal muscle. (Scow.)

Other laboratories reported that testosterone had a marked influence on muscle development, since the temporal muscle in guinea pigs was markedly reduced in size following gonadectomy. Studies in this unit have shown that the other muscles in the castrated guinea pig do not show the same change, and that even though the size of the temporal muscle is reduced, the total amount of myoglobin in the muscle is the same as that in the normal control. Further work has shown that in hypophysectomized rats, the injection of testosterone produces an increase in weight, but that most of the change can be accounted for in the accessory sex tissues. (Scow.)

Nutritional Studies on Man. A clinical study has been made of a lesion in the buccal mucosa which has frequently been mistaken for leukoplakia. A complete histological description of the lesion has been prepared. The lesion also appears to occur in the larynx and vagina. Extensive nutritional studies showed that even though the lesion is frequently seen among malnourished individuals, supplementation of the patients' diets with all of the known vitamins, yeast, and liver extract produced no improvement in the condition. (Sandstead.)

A study of the height-weight records of school children is being made with the Board of Education of Philadelphia. These records have been analyzed to see whether the economic depression of the early 30's had any influence on the growth of school children. The study so far has confirmed the work of others showing that children in the wealthier districts are taller and heavier than children of the same age in the poorer districts. In spite of an improvement in the economic conditions, these differences have been maintained. There also appears to be a progressive increase in the weight of first grade school children over the past 30 years for all the economic groups studied. (Hundley and Mickelsen.)

The study on the seasonal weight gains in children (a cooperative project with the Georgia Agricultural Experimental Station) has shown that both boys and girls gain weight most rapidly in the late fall and early winter and least (and in some cases actually lose weight) in the late spring and early summer. The diets of the children showed a positive correlation between the weight gains and the intake of vitamins A and C. When these vitamins were added to the children's diets throughout one winter and spring, seasonal weight gains still occurred. (Mickelsen.)

Section on Endocrinology (Evelyn Anderson, Chief)

Influence of the Central Nervous System and the Endocrine Glands on Metabolism. Further metabolic studies of dogs have furnished additional evidence that midbrain transection can interfere with protein metabolism and cause nitrogen loss from the body. Electrolyte determinations reveal little change in potassium balance, but consistently positive sodium balances after midbrain transection. There is no evidence that the adrenal participates in this disturbance. Hemidecortication was followed by moderate, brief creatinuria, and by nitrogen and potassium loss, accompanied by sodium retention. The adrenal cortex is tremendously stimulated in this procedure. (Anderson, Knowlton, Laqueur, McCann and Rioch.)

Neural Control of the Pituitary. A small area in the hypothalamus, namely, the median eminence, controls the release of ACTH from the anterior pituitary. When this area is destroyed by an electrolyte lesion, the animal (cat, rat) does not respond to stressful stimuli with an outpouring of ACTH and cortisone. This has been tested by measuring cortisone in the adrenal vein blood, and by measuring the drop in the ascorbic acid level in the adrenal glands. (Anderson, Laqueur, McCann, Rioch, Rosemberg and Schreiner.)

Study of the Hormone Production of a Malignant Pituitary Tumor in the Mouse. A biologically pure preparation of thyroid-stimulating hormone (TSH) has been made from a transplanted malignant pituitary tumor of mice. These tumors contain TSH in as high a concentration as do cattle pituitaries. A comparison of the chemical and biological characteristics of TSH from the two sources is being made. (Anderson, Bates and Furth.)

Metabolism of Hexosamine. A method for the determination of hexosamine in blood and tissues has been developed, based in part on the method of Elson and Morgan. The level of food intake in the rat has a direct bearing on the amount of hexosamine in the blood. Starvation causes a marked fall in the level. Plasma and tissue hexosamines increase after stress. (Boas.)

The Bioassay of Cortisone in Blood. A method has been devised for the bioassay of cortisone in blood, using the adrenalectomized mouse as a test animal and measuring the drop in eosinophiles. (Rosemberg and Cornfield.)

The Assay of Insulin in Blood. A method devised for the assay of insulin in blood will significantly measure insulin in quantities as low as 0.000003 unit. The hypophysectomized alloxan diabetic mouse is used as a test animal. The measurement of insulin in the blood of diabetic and other patients will be of considerable value in elucidating the cause of diabetes. (Anderson, Bates, Yenermen and Cornfield.)

Section on Enzymes and Metabolism (Arthur Kornberg, Chief)

Carbohydrate metabolism (Horecker, Klenow, and Smyrniotis). Previous work has demonstrated the synthesis of pentose from hexose phosphate and the existence of a cyclic mechanism whereby hexoses are regenerated from pentose. This pathway of carbohydrate breakdown has now been shown to be widely distributed in animal and plant tissues and in microorganisms, and is probably of fundamental importance in cellular metabolism. As a result of work in this laboratory, this cycle can now be represented as follows: hexose phosphate → phosphohexonic acid → pentose phosphate → heptose phosphate → hexose phosphate.

Evidence has been obtained for the formation of a tetrose (erythrulose) in the conversion of the pentose (ribulose-5-phosphate) to the heptose (sedoheptulose-7-phosphate).

A new type of reaction has been discovered in the conversion of heptose phosphate to hexose phosphate, in which the dihydroxyacetone group is transferred from sedoheptulose phosphate to triose phosphate. The enzyme has been named transaldolase. A new tetrose, erythrose phosphate, is formed in this reaction.

These tetroses may be of great significance in carbohydrate metabolism. New methods for the preparation and analysis of these sugar esters have been developed.

Nucleic Acid Metabolism (Heppel, Hillmoe, Kornberg, and Lieberman). The role of orotic acid in pyrimidine synthesis has been clarified. A reversible system for the conversion, orotic acid ⇌ dihydro-orotic acid ⇌ ureidosuccinic acid, has been isolated from bacterial extracts. This is the first demonstration of ring closure to form the pyrimidine ring, a fundamental component of nucleic acids. Nucleic acid structure is also being investigated with the aid of specific enzymes. New enzymes have been isolated from intestine and spleen with well defined substrate specificities which will permit a characterization of the bonds present in nucleic acids and polynucleotides. The structure of Streptolysin S will be investigated with these newly developed tools.

Phospholipid Metabolism (Hayaishi, Kornberg, and Pricer). The studies on phospholipid synthesis have progressed to a point which permits a clear definition of the important steps. It has been established that fatty acids are activated by the formation of the acyl-coenzyme A derivatives which have been isolated and identified. The energy is derived from ATP, which is converted to AMP and inorganic pyrophosphate. In the presence of another enzyme fraction, the acyl-coA reacts to esterify a - glycerophosphate. Both mono- and di-acyl phosphatidic acids have been identified as reaction products. This type of fatty acid activation is of significance not only for phospholipid and neutral fat formation, but also for fatty acid oxidation. Phospholipid degradation has been shown to proceed stepwise by the successive hydrolysis of the fatty acid and phosphorylcholine bonds.

Section on Fractionation and Isolation (John C. Keresztesy, Chief)

The Section on Fractionating and Isolation is composed of three parts: (1) fractionation and isolation unit, (2) nutritional microbiology, and (3) large-scale laboratory. It is mainly concerned with the isolation of vitamins, growth factors, and related products from natural materials.

The citrovorum factor, which had been demonstrated to be different from the synthetic product tetrahydro-formyl-pteroylglutamic acid, was isolated from horse liver in crystalline form. Our findings confirmed the identity of natural citrovorum factor with the 1L form obtained by resolving the synthetic product. (Keresztesy and Silverman.)

An extended study was made to develop a method for obtaining maximum yields of citrovorum factor from tissues. As a result, a procedure was established for obtaining citrovorum factor from liver in yields far in excess of those reported in the literature. (Keresztesy and Silverman.)

A product which appears to be intermediate between tissue-bound folic acid and citrovorum factor has been isolated from horse liver digests. It has many of the properties of synthetic formyl folic acid. (Chang.)

The urinary glutamate derivative has been obtained in crystalline form and shown to be a derivative of glutamic acid containing equivalent amounts of glutamic and formic acids and ammonia. (Silverman.)

The large-scale laboratory has extended its help to other groups at the Institutes whenever large volumes and amounts of material required processing. (Keresztesy.)

LABORATORY OF PATHOLOGY AND PHARMACOLOGY

This laboratory (Ralph D. Little, Chief) includes two groups, one concerned with morphologic, the other with physiologic and biochemical approaches. The latter comprises a section on Pharmacology and Toxicology, concerned with studies on the pharmacology and physiology of shock, of certain amines, of antibiotic chemotherapy in leprosy, and of nerve conduction; and a section on Metabolic and Degenerative Diseases; concerned with isolation and characterization of protein and lipoprotein macromolecules, the thermodynamic properties of chronic phosphates, and the isolation and characterization of immunochemical entities.

The morphologic group comprises sections on Pathologic Anatomy, Comparative Pathology, and Pathologic Histochemistry, whose primary function is the morphologic, histologic, and histochemical characterization of naturally occurring and induced disease processes, and the use of this approach to interpret the results of experimental procedures in the fields of infectious diseases, toxicology, pharmacology, and nutritional disease. The section on Comparative Pathology studies spontaneous diseases of laboratory animals, radiation injury, neurotropic virus diseases, mycobacterial infections, and conducts cooperative investigations with other Institutes and Laboratories.

The section on Pathologic Anatomy studies human and experimental pathology, with reference to correlation of clinical studies on disease processes and evaluation of animal research on infection processes, poisonings, physical injuries, dietary deficiency, and endocrine diseases. The section on Pathologic Histochemistry adopts chemical reactions to histologic study, and attempts to evaluate traditional histochemical staining procedures for use in the study of disease processes.

Section on Pathologic Histochemistry

R. D. Lillie is chief of this section. The research program in histochemistry (R. D. Lillie, R. Bangle, and J. Longley) has been devoted largely to the adaptation and development of histochemical reactions, and to exploration of their significance. The project on the study of sudanophilia of leucocytes has developed the finding that a stable sudanophilia not due to the presence of fats can be demonstrated, and that this property is not due to leucocyte benzidine peroxidase. In the studies of ceroid, at least two reactions for unsaturated compounds have been developed, and it is believed that the coincident presence of peroxides can be demonstrated. The Golodetz-Unna ferric ferricyanide reduction test has been evaluated in vitro, and it now appears possible, by appropriate collateral tests, to evaluate much more closely its histochemical significance.

Systematic studies of the histochemistry of the following have been or are being made: the retina, the pigments, hair, ceroid, and other acid-fast substances; thyroid colloid, chromaffin, and entero-chromaffin; and myoblastoma and certain cutaneous diseases in man. Some further progress has been made in the study of histochemical reactions of ground substance and connective tissue fibers.

A method for demonstration of certain water-soluble polysaccharides was evolved and used in the study of the fate of parenterally administered dextran. Observations on acid extraction of tissue components during decalcification were extended to evolve a differential procedure for extraction of ribonucleic acid from sections.

Section on Pharmacology and Toxicology (Sanford M. Rosenthal, Chief)

Mechanism and Therapy of Experimental Shock (S. M. Rosenthal, H. Tabor, R. C. Millican, E. F. Stohlman, J. Stopak). Determination of the fate of saline solutions administered in the treatment of shock revealed that nearly all went into the injured areas, in the form of increased swelling. Administered plasma had the same fate. This requirement for swelling explains why such large quantities are needed in treatment, and why saline solutions are necessary in this form of shock, even though plasma is administered.

The criteria for evaluation of therapy of shock are usually based on improvement in the circulatory impairment. The acute circulatory response to a given therapy was found to be unreliable as an index of its ultimate value in saving the animal. Effective treatment with saline had slight immediate effect on the circulation, although beneficial effects were demonstrable in 4 to 8 hours.

Plasma and certain plasma substitutes were found more effective when given over a period of hours instead of in one or two doses. A beneficial effect not due to sodium solutions was thus demonstrated.

Perritin has been ascribed a role as a causative agent in shock. No deleterious effects, however, could be shown from its administration to shocked animals.

Certain plasma substitutes were found to possess toxic effects in shocked animals, that were not demonstrable upon normal animals. This suggests the value of using shocked animals as an additional assay for their toxicity.

Methods for studying delayed deaths from extensive burns were standardized in mice. Massive doses of antibiotics and sulfonamides prevented death in about one-third of the animals. This, along with bacteriological studies, indicated that infection with bacteria of low virulence plays a role in these deaths.

Metabolism of Certain Amines and Amino Acids (H. Tabor, A. Mehler, E. Adams, H. Bauer, R. C. Millican, S. M. Rosenthal). Histamine was shown to be converted to imadizol acetic acid in vivo and in vitro. The pathways of this reaction were elucidated with purified enzyme systems and were shown to be physiologic, by means of C^{14}-labelled histamine. The acetylation of histamine was shown to occur in the animal body, and not exclusively in the intestinal tract, as suggested by other workers. Acetylation of other amines (noradrenaline, tyramine) by purified systems has been accomplished.

Histidine was shown to be converted to urocanic, and then to L-glutamic acid, using enzyme systems from liver and from bacteria. A glutamic derivative, isomeric with formyl isoglutamine, has been crystallized as an intermediate in the breakdown of urocanic acid by enzymes from liver. The various steps in the breakdown of histidine are being studied with the use of purified enzymes.

The relationship of this process to folic acid deficiency has been demonstrated in experiments with Silverman and Daft.

Histidine biosynthesis: Histidinol, an intermediate in the synthesis of histidine by bacteria, was shown not to replace histidine in rat nutrition.

Spermine, a naturally occurring amine, was shown to produce kidney tubular damage in very small doses. Methods for study have been worked out, and the relation of this finding to kidney function and the kidney disease is being studied. The distribution, metabolism, and excretion of spermine is being investigated.

Chemotherapy (J. Strominger, M. Zalokar, Y. T. Chang). Certain nucleotides (uridine) accumulate in staphylococci when acted upon by penicillin. It has been shown that other antibiotics also produce this, and their chemical identity is being established. Evidence with C^{14}-labelled compounds indicates their relation to nucleic acid synthesis. These findings may contribute to the mechanism of action of antibiotics.

An improved method for the assay of chemotherapeutic agents in leprosy has been developed, employing mice. The isonicotinic acid derivatives were much more effective than other drugs, although activity was demonstrated for streptomycin and certain sulfones. Tibione and other antibiotics were inactive.

The anti-tuberculous activity of spermine is under investigation.

Cellular Pharmacology (A. M. Shanes, M. Berman, E. W. Emmart, E. L. Jackson). The relation of potassium and sodium to nerve conduction has been extended by the use of radioisotopes. The relation of the nerve sheath, and the extracellular space in the nerve trunk, to ion movement and the electrical phenomena of conduction is under investigation. Two veratrum alkaloids, veratridine and cevidine, gave different electrical responses and different responses of potassium release. The relation of ions to impedance changes was studied upon invertebrate nerves.

The production and characterization of muco-polysaccharides in tissue culture and in the cock's comb are being investigated. Enzymes and histochemical methods are being employed to study the ground substances at a cellular level.

Chemical synthesis of a thyroxin isomer (meta) is in progress. Some intermediates or the final product may be of interest as antimetabolites.

Section on Pathologic Anatomy (James H. Peers, Chief)

The work of this section consists of the gross and microscopic study of disease processes in human tissues submitted for diagnosis by various medical installations of the Federal Government; the training of junior medical officers in pathology; and the morphological investigation, both independently and in cooperation with other units of NIH, of lesions in experimental animals produced by viruses, animal parasites, toxic chemicals, reduced atmospheric pressure, dietary deficiency, and endocrine imbalance.

During the report period, the tissue processing laboratory, operated as part of the project and used on occasion by other members of NIH staff, prepared sections of 6,381 animals, 3,376 surgical specimens, and 138 human autopsies.

Among the more interesting results of these investigations, the following may be mentioned:

Production of morphologic evidence that the so-called granular cell myoblastoma of man arises from a cell as yet not identified in the nerve sheath, and not from striated muscle, as its name implies. (Bangle.)

Propagation of a strain of Group A Coxsackie virus in the embryo chick, with production of muscle destruction similar to that in the suckling mouse, which is extreme in degree but not lethal, and with the new development of dermotropism with extensive degeneration of skin and feathers. (Peers.)

Propagation of mumps virus by intracerebral inoculation in suckling hamsters and mice, with production of a characteristic encephalitis. (Peers.)

Production of vegetative endocarditis in rats by repeated exposure to low atmospheric pressure. This endocarditis can be made bacterial by intravenous inoculation of streptococci, and thus provides a tool for the investigation of problems of pathogenesis and antibiotic therapy of bacterial endocarditis. (Highman.)

Investigation of the neurosecretory material, as brilliantly shown by the Gomori technic, in the cells and fibers of the hypothalamic nuclei and neurohypophysis, leading to a suggestive correlation of it with the antidiuretic hormone, and to a clearer demonstration of the fiber tract connections among the hypothalamic nuclei. (Laqueur.)

Section on Metabolic and Degenerative Diseases (R. R. Williams, Chief)

The work of this group is concerned with normal and abnormal physiology, with particular emphasis on the isolation and characterization of macromolecules of interest in these fields. Most of this effort has been concerned with proteins, lipo-proteins, and lipids, though some carbohydrate investigation will be continued, with a view to investigating polysaccharides of biochemical and immunochemical importance.

The research programs of the group have been along nine general lines. Two of these, the program on experimental atherosclerosis headed by

Joseph Bragdon, and that on platelet physiology in relation to the coagulative defects in radiation injury and thrombocytopenic purpura, have become inactive due to the transfer of Bragdon to the National Heart Institute and the resignation of G. H. L. Dillard, who was collaborating with George Brecher of this Laboratory. Bragdon's activities will be described in the National Heart Institute report. Dillard's work on platelet separation has made available a stable preparation of animal platelets of several species for transfusion. The method of preparation and results of some transfusions have been published with Brecher and Cronkite. The project is being continued by the latter two men.

The other seven programs are either active or completed. These consist of the investigations of H. A. Saroff, which fall into two main headings. The first is the development of new methods for the separation and isolation of proteins and other macromolecules. Work on the continuous diffusion method has been completed for the present and been published. This permits large-scale dialysis and diffusion separation of proteins, peptides, and other molecules in the large and intermediate size range. Work is now in progress on the study of conditions under which mixtures of protein species may be separated by foaming. Good progress has been made toward the separation of artificial albumin and gamma globulin mixtures controlled by electrophoretic and ultracentrifugal analysis.

The second major phase of Saroff's work has been concerned with the study of reactive end groupings on protein molecules by chemical blocking or modification methods. Studies on the structure of bovine albumin by methylation of various groups have been concluded in one phase, and a second phase is about to be concluded with a publication on the properties of methylated albumins as studied by methoxyl, electrophoresis, sedimentation analysis, and infra-red spectroscopy in collaboration with H. Scheraga of Cornell University. Immunochemical studies on these modified proteins are being carried out by David Pressman of the Sloan-Kettering Institute for Cancer Research. Further studies of this sort are planned.

An important development resulting from this work was that the ester linkage absorbing at $5.76\,\mu$, shown to be present in methylated albumin, was also found in serum from atherosclerotic patients by investigators in the National Heart Institute. Saroff's work provided an immediate interpretation of this finding and made available a technique for studying the problem.

In addition, he has interested Richard Simpson of this Section in the polarography of the noble metals - first, as a method of determining these metals in heavy metal complexes with proteins and amino acids, and second, to contribute to the analysis of some gold thio-sugars being prepared by A. T. Ness for metabolic studies on gold thio-glucose obesity in mice, in collaboration with Brecher. This phase has been largely completed and is ready for publication. Also with Ness, a paper on the polarography of chromium has been published.

Simpson is pursuing a related program concerned with determining, by polarographic methods largely developed by Saroff, in what manner the affinities of metals for functional groups of amino acids are modified by their incorporation into proteins. The reaction of zinc and cadmium with ovalbumin are being studied. Insulin studies are projected as soon as certain difficulties with the insolubility of these complexes can be overcome.

R. R. Williams with the assistance of S. S. Stone has continued his study of the reactions of proteins with cellulose in relation to the paper strip and column chromatography of proteins. The effects of ionic strength of the protein solvent have been studied, with promising results for the adsorption and elution of proteins from cellulose columns. These basic studies have led to a second and larger phase related to the immunochemistry of proteins adsorbed on cellulose.

From studies demonstrating that successive layers of antigen and antibody could be bound to cellulose irreversibly, the techniques of immunology and chromatography are being applied to the purification of the Newcastle virus. By means of antibodies to normal allantoic fluid proteins adsorbed on cellulose columns, normal allantoic fluid proteins have been removed from ultracentrifugal sediments of Newcastle virus grown in chick embryos. Characteristic ultraviolet absorption spectra have been correlated with virus-active and virus-inactive fractions from cellulose-antibody columns. Further characterizations by immunochemical, electrophoretic, sedimentation, and electron microscopic studies are in progress.

F. Irreverre with the assistance of W. Martin has concentrated his efforts on paper chromatographic analysis of amino acids and their guanidated and methylated derivatives. An improvement in the Williams-Kirby ascending technique has been perfected permitting greater flow distances for solvents, thus permitting greater resolution of components of amino acid mixtures. A new chromatographic technique is about ready for publication. The method simplifies and adds versatility to the general methods, permitting anay degree of resolution possible with the given solvent, with high reproducibility.

A new protein isolated from normal human urine by Dillard and Saroff was chromatographically analyzed. Seventeen amino acids were found.

In the general field of reactive-end-group study of proteins, Irreverre has prepared N-guanido derivatives of 14 amino acids, of which guanido-isoleucine is a new compound. These are being characterized with respect to R_f values. It is planned to guanidate proteins for detection of reactive end groups chromatographically.

With H. Miller of the Naval Medical Research Institute, a cooperative study of the nitrogenous excretion products of mosquitoes by extraction and chromatographic methods is being worked out, with a view to correlation of metabolic changes in mosquitoes with induced immunity to malarial parasites. Large amounts of histidine and uric acid have been found in excreta after blood meals.

A. T. Ness, with the assistance of R. L. Evans, has completed and published studies on the thermodynamic properties of chromic phosphate, hexahydrate and anhydrous. Several new chromic phosphates were prepared. During the past year, an attempt to synthesize several aurous thio-sugars for collaborative trial by George Brecher on a mouse obesity project has met with little success, but has produced some new synthetic routes and thio-sugar intermediates in the synthetic attempts. Glyceraldehyde has been synthesized by a new route for metabolic studies in mice. The possible usefulness of 2-5 methylene d-mannitol for the preparation of D-glyceraldehyde and its derivatives was studied.

Section on Comparative Pathology (William T. S. Thorp, Chief)

The staff of this Section conducts investigations in animals on the pathology and pathogenesis of radiation injury, mycobacterial infections, comparative pathology of neurotropic viruses, and diseases of laboratory animals. Cooperative investigations on the tissue pathology phases of projects in other laboratories and branches of the Public Health Service are carried out.

The research for the period covered here can be grouped into the following three spheres of activity:

I. Tissue studies are being made to determine if any floride toxicity resulted from daily oral dosages. Newly developed methods have yielded information on the pathogenesis of the Rous sarcoma tumor, with particular emphasis on the early stages. The purification of Newcastle disease virus by a chromatographic column has been followed by studies to determine its altered biological activity, and the same technique will be applied to the Rous sarcoma virus. Cooperative studies on nutritionally produced liver pathology have continued. The pathology of Q fever is being studied in detail on cases from controlled field conditions. In this more general group of activities would be included the various minor cooperative studies of rather short duration - i.e., leprosy biopsies (100), examination of animal tissues for histoplasma organisms, and other similar activities. (W. T. S. Thorp, L. N. Loomis, R. T. Habermann, G. L. Fite.)

II. Much effort and attention has been given to the importance of platelets in the hemorrhagic syndrome of radiation injury and to techniques on platelets. It has been shown that the hemorrhagic tendency in irradiated dogs can be prevented by maintenance of a normal platelet level by daily transfusion of concentrated platelets. Improvements have been made on the method of counting platelets in circulating blood, giving consistent results in man. Species differences in the susceptibility of bone marrow to radiation injury have been established, and have been shown to account for the difference in susceptibility to whole-body irradiation. In other studies, continued observation on obese mice shows that obesity did not reduce longevity. (G. Brecher.)

III. The project on diseases of laboratory animals conducts research work on bacterial, viral, and parasitic diseases, to enable investigators to distinguish between the pathology produced experimentally from that produced by the naturally occurring diseases in NIH animal colonies. Effective methods for the prevention and control of these naturally occurring diseases are being developed.

This project has been very active, and much progress has been made in determining the disease problem in the NIH colonies. This has been a cooperative project between this Section and the animal production colonies of the Laboratory Aids Branch. The following diseases have received particular attention: (a) coccidiosis of rabbits, (b) lymphadenitis of guinea pigs, (c) middle ear infection and bronchiectasis in rats, (d) external and internal parasites of all the laboratory animals, (e) bartonella infection in rats, and (f) eperythrozoonosis of mice. Studies have been made on outbreaks of disease in the various NIH laboratories. (R. T. Habermann.)

EXTRAMURAL PROGRAMS

The extramural activities of NIAMD (Ralph E. Knutti, Chief) include the administration of research grants, research fellowships, and clinical traineeships in arthritis and the metabolic diseases. In the administration of the grants and fellowships, assistance is received from the Division of Research Grants, NIH.

Research Grants

During fiscal 1952, 134 grants amounting to $1,388,396 were recommended by the National Advisory Arthritis and Metabolic Diseases Council and approved by the Surgeon General. Approximately one-third of the grants were awarded for projects relating to arthritis, and the remainder aided investigations in the field of metabolic diseases, including metabolism, nutrition, liver diseases, and diabetes.

The projects relating to arthritis have resulted in notable progress along several lines. Scientists in various institutions including William T. Robinson, NIAMD grantee at the University of Michigan Medical School, have worked out safer cortisone dosage schedules. Since prolonged high cortisone dosage may result in facial changes, hirsutism, elevated blood sugar, skin pigmentation, and gastric ulcers, it has been necessary to seek means of treating arthritis which would minimize the side effects. As a result of these studies, much smaller doses are now given, interspersed with rest periods of several weeks. There is hope that the danger of prolonged cortisone therapy can be eliminated.

Joseph Hollander at the University of Pennsylvania has demonstrated the remedial effect of hydrocortisone (compound F) in arthritis, by injecting this substance directly into affected joints.

In the field of nutrition, Grace A. Goldsmith at Tulane University School of Medicine has developed tests for determining nutritional status with regard to the antipellagra and antiberiberi vitamins. These tests are of importance as a means of evaluating dietary needs.

Dr. Jean Mayer at Harvard School of Public Health has developed a strain of mice in which hereditary obesity is prevalent. Studies of these animals have revealed important information on the voluntary selection of nutrients and on the inheritance of diabetes.

Two projects are expected to contribute inestimably to our understanding of the mechanism of action of the adrenal cortical hormones, compounds, B, E, and F. These grants to Charles Huggins, of the University of Chicago, are supporting the synthesis of forms of those compounds in which a radioactive carbon atom will be introduced. These radioactive hormones will be used in tracer studies to help explain their distribution, action, and fate.

Research Fellowships

Of the 192 applicants passed by the NIH Central Qualifications Board and referred to the NIAMD Specialty Board, funds were available to pay only 38.

Clinical Traineeships

The program for training physicians in arthritis was announced in January 1951, and by the end of the fiscal year, funds had been encumbered for 14 trainees, representing the total number that could be supported within the budget.

RESEARCH BY CLINICAL INVESTIGATORS

The Evaluation of Long-term Cortisone Therapy in Rheumatoid Arthritis

Since July 1949, 78 patients with rheumatoid arthritis have been treated with cortisone or ACTH at New York University-Bellevue Medical Center, under the supervision of Joseph J. Bunim. The purpose of this study, which is continuing under Bunim, is to evaluate the use of cortisone in rheumatoid arthritis, to arrive at dependable criteria for the selection of cases suitable for hormone therapy, and to determine the nature, incidence, and seriousness of the side effects from this type of treatment.

The duration of therapy varied from 3 to 42 months. Twenty-nine patients of this series are still receiving cortisone. Fifteen patients have had a remission and no longer require hormone therapy. The remissions have lasted thus far from 3 to 24 months. Of the 29 patients who are still receiving cortisone, about half have been markedly improved and half moderately improved.

The cortisone is purchased with funds from a grant made by the Public Health Service. The rest of the study is supported by an outside grant.

The Epidemiology and Incidence of Arthritis in Industry

Accurate and reliable data on the incidence in this country of the clearly defined types of arthritis in industry are not available. It was decided to select an industrial concern whose medical records are satisfactory, and to analyze carefully the clinical and laboratory records and X-rays in order to determine the prevalence of various types of arthritis and its relation to age, sex, and type of work. The number of days lost as the result of these disorders will also be determined. In accordance with an agreement made by Dr. Russell Wilder, this project is supported by a grant from the Arthritis and Rheumatism Foundation, and the services of Dr. Bunim are utilized in a consultative capacity. The first company to be surveyed is the New York Consolidated Edison Company.

Thus far, 500 cases have been studied. By July 1, 1953, analysis of 1,500 cases will have been completed. These 1,500 cases are the patients who have been absent from work because of musculoskeletal disorders during the five-year period from 1947 through 1951. A total of 21,000 workdays were lost. The average number of employees during this period was 25,000.

Studies in Diabetes

Hyperglycemia due to excess insulin administration. - This phenomenon, which has occasionally been observed among diabetics, is characterized by massive glycosuria alternating with minimal glycosuria (cyclic glycosuria), a greater amount of glycosuria before rather than after meals, and abolition of cyclic glycosuria by decreasing insulin dosage. (Perkoff at Utah.)

A method for measuring the hyperglycemic factor in insulin has been developed. Work is now being done on the development of a test sensitive enough to detect this factor in the serum of normal and diabetic patients. (Perkoff at Utah.)

Treatment of diabetic ketosis. - In diabetics with ketosis the relative efficacy has been tested of the administration of (a) insulin alone, (b) insulin plus intravenous glucose, (c) insulin plus intravenous fructose, and (d) fructose alone. It has been observed that insulin alone or fructose alone is less antiketogenic than a combination of insulin with either glucose or fructose. It has further been observed that fructose is retained within the cell to a greater extent than glucose, resulting in less glycosuria, less hyperglycemia, diminished diuresis, and earlier replenishment of liver glycogen. (Rosecan at Washington University, St. Louis.)

Liver Function and Liver Diseases

Hepatic hemodynamics and their effect on hepatic cellular function. - The effects of (a) apresoline (a vasodepressant), (b) pyrogenic reaction, and (c) hemorrhage, on the hemodynamics of the liver and on liver function have been determined. Alterations in hemodynamics were determined by measurements of the hepatic blood flow, splanchnic blood volume, cardiac output, and renal blood flow. The effect on hepatic function was measured by bromsulphalein extraction and by arterialhepatic vein oxygen difference. It was found that apresoline and pyrogenic reactions caused an increase in splanchnic volume and a decrease in hepatic function. Non-fatal hemorrhage caused a fall in hepatic blood flow and an increase in bromsulphalein extraction and arterial-hepatic vein oxygen difference. (Marks at Columbia University.)

Metabolic changes occurring in liver disease and in hepatic coma. - It has been observed that serum sodium and chloride are depressed in patients with liver disease who have ascites and edema. Plasma volatile base (presumably ammonia) was found to be elevated in cirrhotics as compared to normals, and more so in patients who are in coma. An elevation in plasma glutamine has been observed in some of the patients with hepatic coma. Serial determinations, however, have shown that this elevation occurs relatively late in the course of hepatic coma, and is accompanied by a roughly proportional increase in total alpha-amino acids. This would suggest that plasma glutamine concentrations do not reflect any specific alteration in ammonia metabolism, but rather reflect a general alteration of amino acid metabolism. (Seegmiller, Schwartz, and Phillips at Thorndike Memorial Laboratory.)

New tests for liver function. - The possibility of impairment of transmethylation in patients with liver disease has been investigated by measurements of the excretion of guanidoacetic acid. Another study consists in determining the effect of liver damage on the erythrocyte content of triphosphopyridine nucleotide (TPN), diphosphopyridine nucleotide (DPN), and nicotineamide mononucleotide (NMN). Patients with liver damage have shown, in the red cell, normal values for DPN, but less TPN and much more NMN and total pyridine nucleotide than have healthy subjects. (Hershenson, at the University of Pennsylvania.)

Studies in Renal Function

In this area of investigation, the following projects are under way:

Effect of glomerular filtration rate upon bicarbonate reabsorption and solute excretion; variation in glomerular filtration rate as affected by ion excretion (Thompson at Cornell University; the effect of reducing renal blood flow on urine concentration effect of Pitressin on electrolyte excretion under conditions of hydration and dehydration in human subjects; effect of increased dietary protein on chronic renal disease; diuretic effect of carbonic anhydrase in edematous patients (Isselbacher and Laster at Massachusetts General Hospital); and renal clearance of endogenous phosphate in hyperparathyroidism. (Hiatt at Cornell University.)

Thyroid Function

A study is being done on the mechanism of iodide binding by homogenized rat thyroid gland and the distribution of bound iodide in various amino acids of thyroid protein. (Laster at Massachusetts General Hospital.)

In an investigation of the effect of ferritin (VDN) on renal function in dog and man, it is postulated that VDM may have an antidiuretic effect probably mediated through the neurohypophysis. (Hiatt at Cornell University.)

Phosphorus Metabolism

The effect of oral administration of calcium or strontium on phosphorus absorption has been studied. It has been claimed by others that strontium precipitates phosphorus in the intestine and thereby inhibits calcification, resulting in "strontium rickets." Using P^{32} in rats, it was found that absorption of phosphorus was the same regardless of whether calcium or strontium was fed. (Hiatt at Cornell University.)

Studies on Blood and Blood Diseases.

Hemoglobin synthesis. - Synthesis of hemoglobin in the bone marrow of man and rabbit in vitro is being measured by determining the rate of oxygen utilization and porphyrin formation. This is done with the aid of the following isotopes: C^{14} acetate, C^{14} or N^{15} glycine, Fe^{59} hemin, and C^{14} globin. (Peterson at Peter Bent Brigham Hospital.)

Blood platelets. - It has been observed that transfusion of whole blood or platelets from patients with thrombocytopenic purpura to normal persons resulted in a reduction of the platelet count. Attempts are being made to define and clarify the diverse types of platelets in the blood of man. It is now apparent that probably 8 different types exist. To pursue this study further, it is necessary to devise an in vitro test for detecting platelet agglutinins. In cases of thrombocytopenic purpura, it has been found that although no natural isoagglutinins exist, immune isoagglutinins develop after repeated transfusions and autoagglutinins occur in many cases.

P^{32}-tagged platelets were transfused to normal animals in order to determine the concentration of radioactive P^{32} in various organs of the recipient. (Harrington, Washington University.)

INFORMATION PROGRAM (W. T. Carrigan, Information Officer)

Acceleration of the research program against arthritis and the metabolic diseases, accompanied by mounting public interest, necessitated the establishment of an information office within the Institute. An information and public relations program was undertaken in mid-December 1951, when a full-time information officer was assigned to the Office of the Director.

The responsibility of conveying information to scientists, physicians, and workers allied with the medical profession was met primarily through the following projects: (1) the writing of several speeches; (2) preparations to distribute a 64-page "Manual for Arthritis Clinics"; (3) participation on committees planning scientific lectures and exhibits; and (4) the issuance of notices to professional journals. The speeches were delivered by NIH administrators before such groups as the American Medical Association, International Vitamin Congress, National Food and Nutrition Institute, and the National Dairy Council. Assistance was given in the preparation of speeches for the Surgeon General.

Contacts with patients, their families, and the general public were made through (1) correspondence in answer to inquiries on various health problems; (2) a short film on the institute laboratories, which was televised in 10 major cities; (3) recorded radio programs on arthritis; (4) cooperative revision and distribution of a 32-page pamphlet, "Arthritis--And the Miracle Drugs"; and (5) the writing of leaflets. In these and similar projects, cooperative relations were established with the Arthritis and Rheumatism Foundation, American Diabetes Association, Department of Agriculture, and other Federal and voluntary agencies.

To reach the public through newspapers and popular magazines, numerous releases were issued, press conferences held, and newswriters given such services as research and review. Fact sheets, histories, and background material for articles on the Institute and its areas of interest were prepared and distributed. Contacts with the press resulted in magazine articles, frequent news coverage, and a newspaper series on nutrition.

In addition, administrative documents were written, such as the annual report (short form for publication), descriptions of selected research accomplishments, and material for budget justification. Continuation of the program, with increasing emphasis on information relative to the Clinical Center, is planned.

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

Pearce Bailey, Director

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NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

July 1, 1951 - December 31, 1952

Introduction

This represents the first annual report of the National Institute of Neurological Diseases and Blindness since its establishment in 1950 by Public Law 692. The activities of the Institute proper, however, only stem back to fiscal year 1952 when appropriations were first made available.

The broad responsibilities of the Institute as defined by Public Law 692 are the conduct and support of research and training in the neurological and sensory disorders - among them, cerebral palsy, multiple sclerosis, muscular dystrophy, epilepsy, and diseases causing blindness and deafness. These and many other conditions affect approximately 20 million persons in the United States, and are the first cause of permanent crippling and the third cause of death. In spite of the fact that they are almost all incurable and untreatable and represent extraordinary economic loss to the nation, the research attack on these problems has been singularly slight.

The first 18 months of this Institute's existence represents an incipient challenge to these disorders. This is to say that each program in research and training has been developed as far as the present budget permits, but there are many signs that such programs have come nowhere near reaching the boundaries of need. Thus a research grant, a research fellowship and clinical traineeship program have been firmly established, but the number of worthy applications for support in each of these areas so far exceeds the amount of support which can be given that it would be impossible to judge our present efforts as more than preliminary measures.

Nevertheless, within the broad context of total effort in this field, the Institute has already made significant contribution. Largely through the research grants program, largest of the Institute's programs, it has been possible to support investigation of problems previously neglected and to significantly bolster research effort which had received only minimum support. The support of ophthalmological research, for example, has increased by one-third the total effort in this field. While it is still too early to expect major achievement to emerge from this program, the early encouraging results (see extramural programs) suggest the value of an intensified research attack.

The Institute's own laboratory research program has been limited by lack of funds and space. Coordinated with the research program of the National Institute of Mental Health, the planning, the selection of key personnel and the initial research indicate that once this program is fully under way it will represent one of the major centers for neurological research in the country. Actual initiation of clinical research in neurology and ophthalmology awaits the opening of the Clinical Center, but specific plans and projects are now clearly marked off.

A limited program of information and education, especially designed to meet the needs of the patient, has also been initiated.

A full appraisal of the Institute's progress must include the establishment of close cooperative relationships with the voluntary health agencies in the field, the professional societies, and the medical schools and universities. These relationships have been significant for the clearer definition of goals, interests and responsibilities. One of its more important achievements has been the activation of fundamental research into the central nervous system as opposed to research into each separate category - a major clarification of research needs which has been symbolized by the establishment of the National Committee for Research in Neurological Diseases, composed of the voluntary health agencies and the neurological professional societies.

INTRAMURAL PROGRAMS (see National Institute of Mental Health)

EXTRAMURAL PROGRAMS

The extramural activities of this Institute were limited in fiscal year 1952 to three general areas: research grants, research fellowships, and traineeships in rehabilitation.

With the budgeted amount of $1,015,000, our Institute was able to support 119 grants in the fields of the neurological and the sensory diseases, while it was possible to support 15 younger investigators with the sum available to us in research fellowships, of $51,400. Traineeships in rehabilitation were awarded for clinical training in the principles and practices of rehabilitation. There were 13 awards made to 9 physicians and 4 paramedical personnel. The total sum available to us for this means of support was $36,000.

RESEARCH GRANTS-IN-AID

During the latter half of fiscal year 1952, there appeared to be several definite trends in research as reported by increased demand for funds to support investigations in certain diseases and conditions. Table I shows that the gross percentage increase in approved funds was in the field of multiple sclerosis and the demyelinating diseases. In the last quarter of the fiscal year, approximately 20.7% of our over-all funds were committed in the support of researches in this area. This was an increase of 12.8% over the amounts committed for similar support at the close of the second fiscal quarter. Research in epilepsy showed an attendant increase in activity in that 12.1% increase in funds approved was shown between the end of the second fiscal quarter and the fourth fiscal quarter of the year.

TABLE I

Disease or Condition	Amount Committed (Percentage) 12/31/51	Amount Committed (Percentage) 6/30/52
Epilepsy	8.3%	14.4%
Cerebral Palsy	3.7%	5.8%
Pathophysiology of various neurological diseases . . .	17.8%	19.1%
Multiple Sclerosis and demyelinating diseases. . .	7.9%	20.7%

TABLE II

Disease or Condition	Amount Committed (Percentage) 12/31/51	Amount Committed (Percentage) 6/30/52
Cataracts	3.1%	3.8%
Congenital Eye Disease . . .	4.0%	3.5%
Glaucoma	6.8%	6.0%
Infections (Including Uveitis, Syphilis, Iritis)	5.5%	5.4%
Pathophysiology of various blinding eye diseases . .	2.0%	1.5%

It will be noted that small increases in research activity were also shown in cerebral palsy and in various fundamental researches in the pathophysiology of several neurological diseases.

This situation is shown to be more or less stabilized in fiscal year 1952 where the blinding eye diseases are concerned, for here Table II shows that there was no remarkable increase or cessation of research activity in any of the fields listed. The greatest increase lay in the field of glaucoma, where .8% increase was shown. All other fields show no increase or a very slight decrease in activity, percentage-wise.

Specific research accomplishments are nearly impossible to identify in the year immediately following their publication. The scientific significance of discoveries can be predicted reliably only after one or more decades have passed since the initial publication of findings. However, several fundamental researches have taken place which are presented as being representative of the research areas, methods, and interests of our many grantees. These are presented in Appendix A with no attempt to extrapolate beyond the immediate findings and conclusions.

The distribution throughout the United States of dollar amounts for research grants in the neurological and sensory disorders is not markedly variant from the so-called general research potential* of the country's regions, except for New England. Here there is a considerable difference between the research potential of the region and actual award of research grants in neurology and ophthalmology shown by Table No. 3. It will be noted also that the percent of all research grants is markedly above the potential established. Whereas, it would be difficult to identify all the variables involved for all programs awarding grants in this region, the consideration of this Institute's grants shows that New England has some of the oldest and best established research departments in both the neurological and the blinding eye diseases. Thus, personnel of experience with serious interest in these fields were awarded grants where in other geographical areas similar personnel with like competence do not exist. The significance of this situation is discussed later in the section dealing with Research Fellowships.

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*Federal Support of Medical Research Through the Public Health Service, American Scientist, 1949, Vol. 37, No. 4, Frank W. Reynolds and David E. Price.

RESEARCH POTENTIAL* COMPARED WITH FUNDS COMMITTED BY GEOGRAPHICAL AREAS

	Research Potential	All Programs % of Total Funds Committed	NINDB Funds by %
New England	11.92	17.62	24.73
Middle Atlantic . . .	27.12	25.10	22.18
South Atlantic	11.01	10.66	13.35
East North Central . .	20.37	17.05	16.79
East South Central . .	2.60	2.24	1.55
West North Central . .	10.00	7.40	6.46
West South Central . .	4.56	3.86	3.09
Mountain	2.24	3.16	2.75
Pacific	10.09	12.96	9.10

RESEARCH FELLOWSHIPS

The Research Fellowships program is administered by the Research Fellowships Branch of the Division of Research Grants. Program responsibility, however, is retained by the Extramural Programs Branch of the National Institute of Neurological Diseases and Blindness relative to support by funds budgeted in the name of this Institute.

Our advisers have been unanimous in informing us that the neurologic and ophthalmic research potential in our country is stringently limited by the lack of training facilities--including stipend support--for younger scholars who might conceivably be interested in research careers. Specifically, the fields of clinical neurophysiology and neuroanatomy have been identified as being shortage fields; whereas, in the blinding eye diseases it is rare indeed to find a laboratory committed to full-time researches upon the eye and its associated structures. In recognition of the needs unmet in these fields, the National Institute of Neurological Diseases and Blindness Specialty Board for Research Fellowships recommended the award of fellowships to 3 predoctoral condidates, one of whom was to undertake training in comparative neurophysiology and to two who were undertaking training in the field of neuroanatomy. In an attempt to provide younger research trained physicians, the Specialty Board recommended 6 fellowships to physicians for training in clinical neurophysiological research techniques and methodologies. In addition, another physician was given support for training in the field of the pharmacodynamics of the ocular vascular system. Three doctors of science were supported in fundamental fields having to do with neuroembryology, "conditioned immunity," and the occurrence of natural metalloproteins in certain enzyme systems as they may be encountered in ocular tissue.

In summary, three predoctoral candidates were supported, and in addition ten postdoctoral candidates received fellowships. Two postdoctorate candidates were specifically interested in ophthalmic research, while the remaining eight were interested in research upon the nervous system.

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*"Federal Support of Medical Research Through the Public Health Service," by Frank W. Reynolds and David E. Price, American Scientist, 1949, Volume 37, No. 4.

TRAINEESHIPS IN REHABILITATION

Traineeships in Rehabilitation was a program new to the National Institutes of Health and was undertaken in another Institute, as well as in the National Institute of Neurological Diseases and Blindness. The funds available to this Institute supported 13 trainees, of which 4 were paramedical personnel and 9 were physicians. The purpose of this program is to provide funds for specialized training in the principles and practices of rehabilitation. Attention and emphasis in this training is given to the necessity for the team concept to function in order to provide total treatment. Therefore, special efforts were made to provide traineeship support only to highest caliber physical therapists, medical social workers, and others who applied. Each physician approved for a traineeship award received clinical training fitting him specifically for a career in rehabilitation. The support given to one physician was a timely and a critical necessity in her career. By means of this support, she was able to achieve certification by the American Board of Physical Medicine and Rehabilitation, and has returned to teaching and research in this field in connection with a university-affiliated rehabilitation center on the West Coast.

INFORMATION AND EDUCATION

Because the neurological and sensory disorders are long-term afflictions, in many cases causing extraordinary social, economic and psychological pressure on the crippled patient and his family, there is special need for literature to the patient, clarifying his condition and the means of handling it. Only slightly less important is the necessity for informing professional individuals and organizations concerning medical developments in this field, thereby assisting in early case finding, diagnosis and treatment of these disorders. Insofar as public awareness affects the patient, the public must learn to face the epileptic, the cerebral palsied and the multiple sclerotic without prejudice and to allow them, where possible, to assume a full, normal position in society.

Both activities and planning during the past year have attempted to meet all these problems in some part. At the present time, the first "popular" pamphlet on multiple sclerosis, produced in cooperation with the National Multiple Sclerosis Society, is on the press. The first draft of a pamphlet on cerebral palsy has been prepared; a project which is being done in cooperation with the United Cerebral Palsy Associations. Work has also begun on the preparation of six dramatic recordings for radio broadcasts on the following disorders: multiple sclerosis, muscular dystrophy, epilepsy, Parkinsonism, cerebral palsy and migraine. These too will be produced with the cooperation of the voluntary health associations concerned.

Two leaflets on multiple sclerosis and epilepsy for the Public Health Service's health leaflet series are in draft.

Major projects planned for the immediate future include a pamphlet on muscular dystrophy and the establishment of a Neurological Bulletin, similar to bulletins sponsored by the Heart, Cancer and Mental Health Institutes, which serve to keep the medical profession informed on latest medical developments in their particular fields.

Information and education has also been disseminated through other, more routine channels; and the Institute has been responsible for the preparation of various materials - including speeches, radio and television broadcasts, press releases, answers to inquiries designed to clarify the role of the Institute, the progress and needs in neurological and ophthalmological research, and the availability of modes of treatment and medical facilities.

APPENDIX A

Hydrocephalus

Dr. William P. Williamson of the University of Kansas Medical Center has developed a method for creating experimental hydrocephalus in dogs and monkeys and has devised a promising surgical procedure - an intercranial ventriculocisternostomy - for the treatment of this disorder.

On five monkeys, on whom this procedure was done (the spinal fluid is drained by polythene tube from the lateral ventricle to the cistern of the lateral recess between the frontal and temporal lobes), four were treated successfully and were surviving six months after the operation. This same procedure has already been attempted on a hydrocephalic infant and an adult, but insufficient time has passed for full evaluation of its success.

Epilepsy

Dr. Louis S. Goodman of the University of Utah has been able to produce experimental psychomotor seizures in rabbits and rats and has developed a new anti-convulsant drug (spiro-3-ethyl cyclopentane barbituric acid) which may be useful in increasing electroshock seizure threshold and in preventing pentylenetetrazole convulsions.

The production of experimental epileptic seizure offers investigators a simple, safe method for testing new drugs and also an opportunity for tracing the causes and mechanisms of epilepsy.

Under the same grant, Dr. Dixon M. Woodbury has shown that desoxycorticosterone, when used in conjunction with familiar anti-seizure drugs, strongly elevates the electroshock seizure threshold in rats. Evidence indicates that the immediate action of the combined drugs was not only more rapid than any single agent given alone, but also that their practical activity was longer - in some cases fifteen times as long. Determination of the efficacy of this mode of therapy is being tested clinically.

Multiple Sclerosis

Dr. Richard Fowler of the University of Rochester, through use of the infrared spectroscope, had discovered the presence of a high level of cyanide in the sera of multiple sclerosis and amytrophic lateral sclerosis patients. Relatively large preliminary studies on eighty patients indicate that cyanide is not present in a variety of other disorders.

This study provides a new tool for the early accurate diagnosis of multiple sclerosis. Its main contribution, however, may lie with the degree of insight it permits towards understanding the basic cause of this disorder and thereby devising specific treatment.

No evidence exists that cyanide is itself the direct cause of multiple sclerosis. It seems likely that the presence of cyanide is intimately linked with the as yet unknown etiological factor responsible for abnormal metabolism of the myelin - the fatty sheath covering the nerve fibers of the brain and spinal cord which is attacked at various points during the course of multiple sclerosis. If this link exists, this investigation represents the first major clue to discovering the biochemical changes which do occur in multiple sclerosis.

In the course of this study, multiple sclerosis patients have received dosages of thiosulfate, a known detoxification agent for cyanide. In all cases where this therapy has been attempted, cyanide has rapidly disappeared from the sera. There has been no evidence as yet, however, that such therapeutic measures can influence the symptoms of multiple sclerosis.

Corneal Grafts

Dr. A. Edward Maumenee of the Stanford University School of Medicine has shown that one of the leading causes for the clouding of corneal grafts is a donor-recipient sensitization, i.e., transplant from one person to another is adversely affected by an as yet undefined allergic reaction.

It has become apparent, however, as a result of these investigations, that opacification of corneal grafts occurs within seven weeks after the operation or it does not occur at all. If, therefore, the graft can be protected from sensitization for six or seven weeks after transplant, a high probability exists for maintaining permanent transparency.

Preliminary experiments with rabbits indicate that sensitization may be eliminated by treatment with cortisone prior to grafting and during the period of allergic reaction. Since the clinical appearance of the ocular reaction in rabbits during clouding is similar to clouding incurred by humans, it is possible that cortisone therapy may resolve a major ophthalmological problem.

Corneal Transport Routes

Dr. Lorvand V. Johnson of Western Reserve University, has discovered the mode of transport by which salt, water and other substances leave the cornea and thereby maintain the cornea in the necessary state of partial dehydration for transparency. Evidence now points to the fact that such material leaves the corneal stroma by the endothelial-aqueous route rather than through the tears, as formerly believed.

The determination of this and other modes of nutrient transfer in the eye is of importance in the understanding of such disorders as glaucoma, keratitis and cataract which are believed to be metabolic disturbances caused by "breakdowns" of these transport systems.

In another study made by this grantee, preliminary results show promise that ethylene diamine tetracetic acid can protect corneal transparency after lime burns.

Brain Tumor

Dr. Joseph H. Globus of the College of Physicians and Surgeons, Columbia University, has produced evidence which suggests the need for modification of the radon implantation procedure as a mode of therapy for brain tumor and other brain growths.

As a result of this study, made on fourteen dogs, it was found that radon seed implant creates damage beyond the area to be attacked for purposes of treatment. Necrosis of cells around the implant occurs for a considerable area as does scarring of the nerve tissue. Just how this cellular destruction and scarring affects brain or motor function, however, has not so far been ascertained.

DIVISION OF RESEARCH GRANTS

Ernest M. Allen, Chief

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DIVISION OF RESEARCH GRANTS

July 1, 1951 - December 31, 1952

INTRODUCTION

The Division of Research Grants serves as the focal point for administration and coordination of all research grant and fellowship activities of the National Institutes of Health. It provides a number of services to the Grants Branches of the seven Institutes, operates a large non-categorical grants program with the advice of the National Advisory Health Council, and awards non-categorical fellowships with the advice of the NIH specialty boards.

The National Institutes of Health research grants program is designed to support the ideas of investigators in non-Federal institutions and is operated in a manner aimed to minimize government control and to maximize participation by the scientists themselves. Decisions as to the awarding of grants depend, therefore, primarily on the advice of the seven National Advisory Councils--one for each Institute--and the technical panels of the Division--the Study Sections--which advise the Councils. Since the roles played by the Division, the Study Sections, the Grants Branches of the Institutes, and the National Advisory Councils are not easily separated one from the other, we will trace the course of a grant application in order to explain the functions of each.

The applicant for a grant--who must be a scientist not employed by the Federal Government--describes his proposed research on a special form and forwards it to the Division of Research Grants through appropriate officials of his institution. (In fiscal 1952, 2,821 applications for research grants were received.) The Division of Research Grants is responsible for preliminary processing of all applications; for the assignment of each application to the appropriate Study Section and Institute; for notification to the applicant as to receipt and assignment of the application and as to probable date of notification of action.

Copies of the application are prepared for distribution to staff members of the Division and Institute, the Study Sections, and the Councils. The Executive Secretary of the Study Section, who is a professional staff member of the Division, obtains necessary additional information and arranges for visits to the applicant in special cases, in preparation for the scientific appraisals furnished by the Study Sections.

The Study Sections meet three times a year, about six weeks prior to Council meetings. They review applications from a standpoint of scientific merit and make recommendation as to approval, disapproval, or modification. Each application recommended for approval is given a tentative average priority rating based on the individual rating of each Study Section member. The Executive Secretary prepares a résumé of the Study Section actions, and responsibility for the applications then passes to the appropriate Institute grants branch for final consideration by the respective Advisory Councils.

The Grants Branch Chief reviews the Study Section recommendations, seeks additional information where necessary, and presents the applications to his particular National Advisory Council, which acts not only on scientific merit, but also from a policy standpoint and with relationship to the over-all

Institute program. The Councils meet three times a year and their actions constitute the basis for final action by the Surgeon General of the Public Health Service, who awards grants in accordance with Council recommendations.

After the award is made, the Division once more assumes responsibility for certain aspects of the administration of the grant by providing fiscal control, audit, and IBM records maintenance. It should be mentioned that the Division also audits and maintains IBM records on all NIH training grants, construction grants, traineeships, and special grants. For research grants, the Executive Secretary of the appropriate Study Section is responsible for obtaining progress reports and final reports from the grantees, as well as for notifying the grantees as to renewal applications.

The Division of Research Grants is responsible also for recommending to the Surgeon General the disposition of inventions made by all NIH grantees, trainees, fellows, and employees; for developing procedures for carrying out this responsibility; and for recommending policies to the appropriate bodies, in accordance with existing Orders.

GRANTS BRANCH FUNCTION OF THE DIVISION

The Division of Research Grants functions as an Institute in the operation of the non-categorical ("G") grants program, using the same procedure followed by the grants branches of the categorical Institutes. It has a separate advisory panel, the National Advisory Health Council, which also serves in a reviewing capacity for the National Microbiological Institute, since the latter has no council of its own.

Because the non-categorical research grants may support investigations in any field related to health, the "G" program serves as a "balance wheel" for the total program. It ensures equity of opportunity for the applicant regardless of his field of interest. It may support projects not falling properly into any of the programs of the categorical Institutes or projects which are of some interest to many of them.

In fiscal 1952, 738 applications for $7,176,194 were assigned to the "G" program. Of these, 543 requests, totalling $4,627,059, were approved for payment.

FELLOWSHIPS BRANCH

The Fellowships Branch of the Division of Research Grants conducts the fellowships program for the National Institutes of Health from funds provided by the categorical Institutes and from a non-categorical fund of the National Institutes of Health. Fellowships are awarded to promising students and scholars in medical research and allied fields on three levels--Predoctorate, Postdoctorate, and Special, and bear the designation of the supporting Institute; or, where the Fellowship falls in the general field, it carries a National Institutes of Health designation. Selection of applicants is made on a competitive basis by one of eight reviewing boards of NIH staff scientists, representing each of the Institutes comprising the National Institutes of Health and one general panel, each of which meets three times a year.

During the fiscal year 1952, the Research Fellowships Branch, Division of Research Grants, received and processed for review 1,555 fellowship applications, totalling a requested $4,642,580 for all Institutes. From these requests it was possible to support only 540 Fellows, involving an expenditure of $1,749,370 for all Institutes. Of the 540 Fellows selected, 300 were Predoctorates, 223 were Postdoctorates, and 17 were Specials. Of these 540 Fellows, 121 were supported by the Division of Research Grants as NIH Fellows. The awards made at the last meeting of the fiscal year reflected a previous policy decision to place more emphasis on the Postdoctorate phases of the program. Implementing a decision made during the fiscal year 1952, the stipends for Fellowships will be increased by $400, beginning July 1, 1952.

STUDY SECTION ACTIVITIES

The technical advisory panels of the research grants program are called Study Sections and are composed of about ten specialists from universities and other non-Federal research institutions, with additional voting representatives from the Army, Navy, Air Force, Veterans Administration, and Public Health Service. The Division of Research Grants provides a non-voting professional staff member who serves as Executive Secretary to the Study Section.

During fiscal 1952, the Study Sections were reorganized somewhat in order to meet changing needs. Several new panels were organized, including the Metabolism and Nutrition Study Section, the Biochemistry Study Section, the Endocrinology Study Section, the Sensory Diseases Study Section, the Committee on Radiation Studies, and the Committee on Standards for Grants Surveys. As of June 30, 1952, the following panels were functioning:

Biochemistry Study Section
Cardiovascular Study Section
Dental Study Section
Endocrinology Study Section
Environmental Health Study Section
Experimental Therapeutics Study Section
Hematology Study Section
Mental Health Study Section (administered by the Mental Health Institute)
Metabolism and Nutrition Study Section
Microbiology and Immunology Study Section
Morphology and Genetics Study Section
Pathology Study Section
Pharmacology Study Section
Physiology Study Section
Public Health Study Section
Sensory Diseases Study Section
Surgery Study Section
Tropical Medicine Study Section
Virus and Rickettsial Study Section
Committee on Radiation Studies
Committee on Sectional Research for Microbiology
Committee on Standards for Grants Survey

The Committee on Radiation Studies was established administratively in April, 1951, by joint action of the Division of Research Grants and the National Cancer Institute. It consists of twenty-two members outstanding in the fields of radiation, physiology, psychoneurology, and radiation physics, who are appointed by the Surgeon General for an indefinite period. The function of the Committee is to review applications for grants-in-aid relating to research projects in radiation biology, with special attention to (1) research leading to an explanation of the post radiation syndrome; (2) research in or on the altered gastro-intestinal physiology which results from exposure to ionizing radiations; and (3) research in the psychoneurobiology of animals as a result of varying exposures to ionizing radiations. The Committee has close liaison with the Atomic Energy Commission.

The Committee on Standards for Grants Surveys was established by the Division to review certain applications for grants which involve surveys. The Committee, consisting of Public Health Service statisticians and non-Federal consultants, will review designated applications after July 1, 1952, and will specify the conditions under which the awards may be made. The necessity for this committee arose when the Bureau of the Budget delegated to the Public Health Service its responsibility for enforcing those provisions of the Federal Reports Act which require that surveys of 10 or more persons, when sponsored by a Federal agency, be approved by the Bureau of the Budget. In its delegation of authority, the Bureau of the Budget exempted clinical and laboratory surveys from this special treatment.

The former Metabolism and Endocrinology Study Section was dissolved in September, 1951, and projects in the field of metabolism were transferred to a new Metabolism and Nutrition Study Section. About 70% of the projects formerly assigned to the Metabolism and Endocrinology Study Section were assigned to another newly established panel, the Endocrinology Study Section, which was formed in fiscal 1952 as an aid to the new grants program of the Institute for Arthritis and Metabolic Diseases. The nutrition projects of the Biochemistry and Nutrition Study Section were transferred to the new Metabolism and Nutrition Study Section and a new study section on Biochemistry was established to replace the former Biochemistry and Nutrition Study Section.

The Sensory Diseases Study Section was activated on October 13, 1951. It was established to furnish specialized scientific review of the increased number of requests for support of research dealing with the sensory organs, and to aid in the review of applications assigned to the newly created Institute of Neurological Diseases and Blindness. The consultants comprising this panel are representative of the specialties in the field of sensory diseases.

In addition to their function of technical review of applications, the Study Sections are responsible for the periodic review of their special fields to detect gap areas and to develop means for stimulating necessary research or for initiating special projects. The following Study Section activities were of particular interest in fiscal 1952:

Research Needs in Tropical Medicine.

Members of the Tropical Medicine Study Section and 38 other scientists met in Washington in September, 1951, to review existing problems in tropical medicine. At this conference it was recommended that research be stimulated in many fields of tropical medicine, but particularly in schistosomiasis, mass control of trachoma, insect resistance to insecticides, and the gastroenteric infections.

Toxoplasmosis.

In August, 1951, the Tropical Medicine Study Section sponsored an *ad hoc* meeting on toxoplasmosis. The group of ten persons, including representatives from the Study Section, grantees, and staff members of the National Microbiological Institute and of the Army, agreed on two major points: (1) serodiagnostic tests have been developed to the point of usefulness whereby they can be handled in a routine manner; and (2) research laboratories should be relieved of this routine burden by establishing a laboratory for this purpose at the Communicable Disease Center, which could provide this service for those States unable to perform the tests. These recommendations were transmitted to the Surgeon General and the recommended laboratory has been established at the Communicable Disease Center.

Radiation Injury.

During fiscal 1952, the National Cancer Institute, in collaboration with the Atomic Energy Commission, undertook a special program in radiation injury with particular emphasis on psychomotor effects in primates. To provide technical advice, the Division established the Committee on Radiation Studies referred to above. This Committee met in September, 1951, to review applications; to establish standards of dosimetry; to draw up general plans for cooperative studies; to outline urgent research problems; and to advise staff members regarding stimulation of research. In January, 1952, in Columbus, Ohio, the Committee sponsored a meeting of grantees, Committee and Council members, to exchange information and to discuss mutual research problems. The results were particularly gratifying and plans are under way to have annual conferences of this nature.

Venereal Disease.

The annual Venereal Disease Symposium, under the joint sponsorship of the Experimental Therapeutics Study Section and the American Venereal Disease Association was held in Washington on May 1-2, 1952. Approximately 273 scientists from the United States attended; thirty-three papers were read and ten others were presented by title.

Artificial Heart-Lung Mechanisms.

In September, 1951, at the National Institutes of Health, the Surgery Study Section sponsored an informal symposium on the current state of development of artificial heart-lung mechanisms. The primary purpose of this symposium was to afford the Public Health Service grantees who are working on this type of research an opportunity to report to the Study Section the advances that have been made in the development of mechanisms to detour blood from the heart so that operations can be performed on the bloodless heart. No formal papers were presented, since much of the work reported is incomplete and involved experiments which are still in progress, but two methods for detouring blood from the heart were reported. One method, which has been used successfully on dogs and may be ready for application to human patients within a year or two, is to detour the blood by a pumping mechanism into an oxygenating apparatus. The second type is the development of a pumping mechanism which will detour the blood from one or both sides of the heart but will use the animal's own lungs for oxygenation. The techniques, when perfected, will facilitate the opening of the various cavities of the heart for direct surgical exposure, thereby enabling direct surgical attack on cardiovascular defects.

Blood Vessel Grafts.

The Surgery Study Section sponsored another symposium at the National Institutes of Health in January, 1952, on blood vessel grafts. Investigators from the departments of surgery of medical schools country-wide were invited. At this meeting six papers were presented covering blood vessel restoration, the use of homologous aortic grafts, experimental vascular grafts, arterial homografts and arterial replacement, and the grafting of small arteries and veins. Problems covered during the general discussion dealt with methods for storage and preservation; relation of length to success of grafting; relation of matching of size to the success of grafting; the degree of curvature permissible in a graft; and related aspects.

Cinefluorography.

A conference sponsored by the Cardiovascular Study Section was held in New Orleans on January 7, 1952, on cinefluorography (X-ray motion picture technique). The meeting was composed of staff members of five laboratories, distributed over a wide geographic area, which are being supported by Public Health Service research grants in the field of cinefluorography. Representatives from related industry were also invited and the Chairman of the Study Section acted as host.

One of the techniques discussed consists of taking motion pictures of an X-ray image on a fluoroscopic screen. Dense tissue (bones and teeth) can be visualized directly, whereas hollow viscera (alimentary canal, heart, blood vessels) can be seen with the aid of radio-opaque media. The use of 70 mm. film constitutes an obvious method of advance in this technique, because the photographic optics of wide film yield better clarity and detail than is possible with the narrower widths. Cameras and lenses suitable for use with wide film are extremely expensive, however, and special equipment must be designed for development and projection.

Another approach to the problem is to apply television (electronic) technique to the amplification of the image on the fluoroscopic screen. By this means, considerable blackening, even on 32 mm. film, can be produced with very low intensity X-rays, so that rather long sequences can be obtained from a patient with no risk whatever. Films made in this way are not as clear, nor do they provide as much detail as the 70 mm. sequences now available. The exposures involved in the present procedure with 70 mm. film, though relatively high, are not prohibitive for human subjects, and can be justified where real diagnostic aid is needed. One factor yet to be cleared up is that the X-ray level is still too high to use in any general way with safety. The investigators present at the conference are convinced that cinefluorographic methods will have important applications in diagnosis, teaching, and research. Research uses are already developing in connection with animal experiments, where protection from overexposure is of less importance than in clinical work.

Colchicine.

A conference for the exchange of ideas between investigators interested in the synthesis of colchicine was conducted by the Experimental Therapeutics Study Section in September, 1951, at the James Ewing Hospital in New York City. Thirty-two people participated, representing American chemists, representatives of foreign laboratories, Study Section members, members of the National Advisory Cancer Council, the National Institutes of Health, and the Sloan-Kettering Institute. The conclusions drawn from this conference indicate that there is great need for a more precise definition of the mechanism of action of colchicine and related compounds on cell growth in order to provide a more rational direction to the synthetic programs; that the chemical studies of colchicine have led to the identification of a unique molecule, tropolone, with real need to investigate its biological activity in systems other than growth inhibition; and that the chemical research on colchicine has intrinsic merit in pure chemistry irrespective of its applicability to practical therapy in malignant disease. So far, there is insufficient evidence that colchicine itself has shown enough inhibitory activity, either on animal or on human tumors, to warrant any conclusions in the latter respect.

Microspectrophotometry of Cells.

The Morphology and Genetics Study Section in September, 1951, sponsored a conference at the Massachusetts Institute of Technology on the Microspectrophotometry of Cells. The conference was designed to discuss the application of recent advances in biophysics and instrumentation to problems of biology, particularly in the fields of cytology and cellular physiology, and to bring together the investigators who, in spite of widely differing points of view, are nevertheless actually working in this field.

SCIENTIFIC ACCOMPLISHMENTS OF GRANTEES

Space does not permit a complete recounting of scientific progress in such a large and diversified program as the one conducted by the Division of Research Grants. The following examples, however, indicate the variety of projects being sponsored.

At Duke University School of Medicine, Dr. Keith S. Grimson is testing patients who have undergone vagotomy for peptic ulcers, for secretory and motor function. A method of gastric motility measurement has been developed which determines completeness of vagotomy and which reliably predicts recurrence of ulcers. A second accomplishment of this work has been the study of new drugs that will selectively block parasympathetic pathways, and in this way effect "medical vagotomy." Studies with Banthine are also being continued; with the use of this drug, operation has been avoided in 40 of 62 patients with indications for surgery. Three new drugs which are potentially better than Banthine are now being tested.

Dr. Folke Skoog, of the University of Wisconsin, is carrying on a program of basic research on the causes of excessive growth of fresh water plankton in lakes, streams, and reservoirs, particularly of bloom-producing blue-green algae. Blue-green algae produce obnoxious odors, kill fish, and may cause the death of farm animals. Methods of isolation and culture of blue-green algae, including data on the requirements of essential nutrients for optimum yields of several of the species in pure cultures, have been published through this research. Practical elimination of blooms of blue-green algae are being explored on a long-term basis by removal of some essential nutrient constituent for limitation of growth or on a short-time basis by the application of highly selective toxic chemicals.

With the support of a "G" grant at New York University, Dr. Severo Ochoa and Dr. Wolf Vishniac have been working intensively on the manner in which the sun's energy becomes available to the plant for the production of sugars and proteins from carbon dioxide and water. The crucial photosynthetic reaction appears to be the cleavage of water by this energy after it is absorbed by chlorophyll. These investigators have shown recently that a compound containing the vitamin, niacin, is involved in this essential splitting of water by demonstrating that illuminated suspensions of green granules from spinach chloroplasts catalyze the transfer of hydrogen from water to coenzymes I and II. The discovery of this fundamental mechanism opened the way to more complete explanation of such important processes as: the enzymatic utilization of carbon dioxide to form sugars and amino acids; and the production of storehouses of energy in the cell in the form of the energy-rich compound, adenosintriphosphate. The main task now is to elucidate the mechanism by which the pyridine nucleotides and other coenzymes are reduced in the light.

At the University of California, Berkeley, outstanding work is being done by another of our grantees, Dr. C. H. Li, who has shown that the ACTH component is a low molecular weight substance, peptide in nature. Published data indicates that the size of the active component is probably in the neighborhood of 1500. By a combination of various techniques, highly potent ACTH fractions, having an activity over 400 USP units per mg., can be obtained from the pepsin digest of ACTH preparations. The following amino acids are found to be absent in the purest preparation: cystine, methionine, tyrosine, serine, isoleucine, and histidine. It has also been shown that there is a lack of correlation between the adrenal ascorbic acid depleting activity and other indices of hyperadrenocorticism of various ACTH active fractions. These data may be explained by the assumption that there are various ACTH components which could be derived from the whole ACTH molecule by chemical modifications.

At the University of California, Dr. Hamilton H. Anderson and Dr. Henry Rapoport are conducting basic studies on the mechanism of analgesia. To date the investigators have isolated and identified five metabolic products of codeine: free morphine, a conjugated form of morphine, free nor-codeine (n-demethylated codeine), a conjugated form of nor-codeine, and a conjugated form of codeine. A sixth metabolite ("codeine-X") has been found in the bile of rats but has not yet been identified. At least two other metabolic products are theoretically possible. Metabolism of morphine and codeine has received considerable attention in the past but the results have led to the assumption that in the normal animal, metabolism is restricted to conjugation with as yet unidentified compound(s), thereby forming "bound" morphine and codeine; the results of the present study have delineated the fact that metabolism of these alkaloids is considerably more complicated than was previously recognized.

Under a "G" grant made to Dr. Gregory Pincus of the Worcester Foundation for Experimental Biology, hitherto completely unexplored aspects of steroid hormone metabolism have been investigated. The study was undertaken to delineate the transformation products resulting from the perfusion of cortisone and related corticosteroids through a variety of isolated organs. It was felt that such studies might serve as a definitive basis for an understanding of how the steroid hormones are synthesized in the body, how they act, and how they are broken down and excreted. Some notable leads have already resulted from this work: (1) the development of new techniques for steroid analysis by paper chromatographic procedures; (2) the discovery that the perfusion of either 11-desoxycorticosterone (DOC) or cortisone through rat or rabbit livers leads to the production of numerous steroidal transformation products; (3) the suggestion through the use of C^{14} labeled DOC that degradation of corticosteroid to non-steroidal products occurs in the liver. These developments provide more adequate methods for chemical studies of steroid metabolites and initiates a search for corticosteroid metabolites possibly having significant biological activity.

Dr. Peter Morrison and Dr. John Ferry, Wisconsin University, have developed physical chemical techniques and data whereby the size and shape of the fibrogen molecule can be established unambiguously. They have detected an intermediate polymer in the conversion of fibrinogen to fibrin and postulate that the polymerization of fibrinogen proceeds by lateral dimerization with partial overlapping giving two parallel end-to-end chains with staggered junctions. The implication is that the bond loci are on the sides rather than the end.

At Western Reserve University, Dr. Arnold Welch has reported development of a new technique of assay for the intrinsic factor in pernicious anemia, using radioactive vitamin B-12. This assay technique should permit rapid advance in the isolation, purification, and identification of intrinsic factor and the elucidation of the mechanism of action.

Dr. Berwind P. Kaufmann of the Carnegie Institution of Washington, Cold Spring Harbor, New York, is studying the nature of the changes in the living cell which are produced by irradiation. Using the newest methods of paper chromatography and cytochemistry, this investigator has been looking into the question of changes in the nucleic acids and the proteins which go to make up the cell. He has found that chemicals which induce chromosomal aberrations also cause dislocation of nucleic acids and proteins. Furthermore, immersion of onion root tips in ribonuclease produces aberrations similar to those caused by chemicals (such as 8-hydroxyquinoline) This work has provided the researcher with a more reliable method for the production of such abnormalities; in turn, this will afford a more critical basis on which to study the mechanism involved in these effects.

The Endocrinology Study Section in March, 1952, in collaboration with several commercial drug houses, undertook the synthesis of radioactive cortisone. Under the guidance of Dr. Tom Gallagher, research on the ring-labeling of cortisone with C-14 has progressed to the point where it will soon be possible to make radioactive cortisone available to qualified investigators, free of charge. A similar project for the biosynthesis of radioactive compounds F and B has proceeded successfully, and ring-labeled progesterone, in small quantities, perfused through beef adrenal glands, has yielded radioactive F and B. This work is largely under the guidance of Dr. Gregory Pincus, a member of the Endocrinology Study Section, and there is every indication that compounds F and B will be available for distribution in a short time, in the manner described for cortisone.

DEVELOPMENTS IN POLICY AND PROCEDURE

Inter-Council Subcommittee on Institutional Grants.

In the spring of 1951, the Surgeon General appointed an Inter-Council Committee on Institutional Grants to study the need for fluid grants and make necessary recommendations. This Committee met in October, 1951, and after a day of discussion established a subcommittee to study research needs throughou the country, to explore the mechanisms by which the Public Health Service migh help to meet these needs and to draft recommendations for implementing desirable changes. The Subcommittee visited a representative sample of universitie (14) where "grass roots" discussions were held on the nature of the problems which had led to the widespread interest in institutional grants. During the course of its investigations, the Subcommittee met with generous and most gratifying approval and endorsement of the prevailing Public Health Service research grants program. Many excellent suggestions for modification and improvement were offered, however, and the findings and recommendations of the Subcommittee were incorporated into a report which the Committee submitted to the National Advisory Councils. As a result of these recommendations, the Public Health Service is exploring the possibility of increasing the allowance for overhead on grants, and is examining the possibility of making grants of fluid funds to supplement the project system. The Councils unanimously recommended establishment of a permanent Inter-Council Committee with representation from each Council. This Committee will serve as a focal point for discussion of Inter-Council affairs and will meet from time to time to consider timely proposals and recommend appropriate action to the several National Advisory Councils.

THE CLINICAL CENTER

John A. Trautman, Director

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THE CLINICAL CENTER

July 1, 1951 - December 31, 1952

ADMINISTRATION

July 1, 1951, Dr. John A. Trautman succeeded Dr. Jack Masur as Clinical Center director.

The Clinical Center officially came into being as an organizational entity January 16, 1952, when the Surgeon General issued Organization Order No. 29 establishing it as a division of the National Institutes of Health. As the year 1952 closed, plans were being made to admit the first patients in April 1953 and to build gradually to an activation of 150 beds by June 30.[1]

At the end of the period covered by this report, construction on the main building was 99.5 percent completed. December 8, 1952, the immediate staff of the director moved into the offices on the first floor. Construction was begun in the summer of 1952 on the last major structure essential to the operation of the Clinical Center patient-care program. This was the housing facility for 24-hour-duty Clinical Center personnel. It was 16 percent complete on December 31, 1952.

The development of an effective organization plan and recruitment of staff to fill key positions was a major activity during the past year.

Because both the welfare of patients and the research autonomy of the seven Institutes were involved, the organizational problem was not an easy one. The Clinical Center director and his principal staff members participated extensively in the numerous surveys, analyses, and discussions involved in this phase of the Clinical Center's development.

While it undoubtedly will continue to be an evolutionary process, the organization form and interrelationships that emerged during the closing months of 1952 were sufficiently firm to permit staff recruitment to go forward in preparation for the opening of the Clinical Center.

Under this plan the Clinical Center director is charged with the full responsibility for patient welfare. Laboratory research operations are a concern of the Clinical Center director only where they may affect the quality of medical care.

A medical board will be established with responsibility to develop broad recommendations governing standards of medical care, to review the qualifications of physicians under consideration for regular and consultant appointments in the medical care program, and in other ways bring to bear the best professional judgments available at NIH in the general field of clinical research. When approved by the Director, NIH, findings of the Board will form the framework within which these activities are accomplished.

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[1] Unforeseen circumstances have made it necessary to postpone opening until July 1953.

The board will consist of chiefs of clinical research from the various Institutes, chiefs of certain central medical service departments of the Clinical Center, and one or more members of the Clinical Center director's immediate medical staff with the director serving as an ex officio member. All appointments to the board are made by the Director, NIH.

Since it would be impractical for each Institute to perform a number of patient-care functions that are common to all, it has been agreed that certain key personnel will function in a dual capacity--to provide a central service to patients of all Institutes and perform research in their particular field as a function of the parent Institute.

Definite organization and staffing arrangements for the Clinical Center which had been started by December 31, 1952, were as follows: nursing, admissions and follow-up, social service, nutrition, and the medical services departments of pathological anatomy, diagnostic X-ray, dental, clinical pathology, pharmacy, and medical records. Medical departments which had not progressed beyond the planning stage were surgery, anesthesia, and rehabilitation.

Most of these departments will have chiefs who will work in a dual capacity of central service and of autonomous research. For example, the Chief, Pathological Anatomy Department, will be responsible to the Director, Clinical Center, for the proper operation of all Clinical Center functions which are assigned to this Department, but he will generally be responsible to an Institute for the conduct of the research he performs in this field.

In the administrative field, a dual responsibility also is necessary in the position of Clinical Center executive officer. For some functions, he is responsible to the director, Clinical Center, and for others, to the Executive Officer, NIH.

The Clinical Center director will be aided in supervision and coordination of these various service activities by two assistant directors, one of whom will be responsible for coordinating the professional service departments. Dr. Robert T. Hewitt, formerly on the staff of the Mental Health Institute, was appointed to this position on July 1, 1952. The other assistant director will guide the remaining activities of nutrition, nursing, social service, outpatient and follow-up departments and serve as acting director in the absence of his superior. Dr. James P. Dixon was appointed to this position, assuming his duties October 1, 1952. Dr. Dixon was formerly Health Officer of Philadelphia, and Director of Health and Hospitals at Denver, Colorado.

Among other functions, the Clinical and Professional Education Branch will coordinate and promote the educational advancement of the clinical and laboratory fellows employed by the various Institutes, a staff category corresponding to the residents of the usual teaching hospital.

Plans for the Patient Inquiries Branch and the Business Operations Branch had not been completed by the end of the period of this report.

A major part of the time of the director and all those staff members on duty during the period of this report was taken up with such matters as changes in design of parts of the building and its permanent equipment, lists and specifications for movable equipment, furniture and supplies. The staff worked constantly and in the closest harmony with the Research Facilities

Planning Branch of the Office of the Director, NIH, the staffs of the several Institutes, engineering and contract personnel of General Services Administration, and the Purchase and Supply Branch of the Office of the Director, NIH.

An equally important activity was the detailed process of planning for scores of positions that will need to be filled before the first patient can be admitted and the closely related recruitment process. The staff worked with the Personnel Branch of NIH and with the Civil Service Examining Board at NIH on these important tasks. It should be recorded that every effort was made to spread our recruitment of professional and technical staff over the entire country.

On the following pages are given reports of the various Departments which had been established and had begun to function during the period of this report.

DENTAL DEPARTMENT

The Chief of the Dental Department, Dr. Ralph S. Lloyd, was appointed July 1, 1952. Prior to that time, in cooperation with the director and staff members of the Dental Research Institute, and of other Service dental officers he had actively participated in planning the various functions that will be performed by the department.

During the calendar year 1952, much time and effort has been expended in selecting and ordering the equipment for the dental clinic. This includes both large and small equipment and the expendable equipment for use in dental procedures. An organizational plan has been developed and job sheets for the various positions within the Dental Department have been completed and accepted. A definite organizational pattern dividing the Dental Department into subdivisions such as Department of Diagnosis, Periodontology, Prosthetics, Oral Surgery, and Operative Dentistry has been formulated. Some plans for future clinical research projects have been considered and will be submitted for adoption as a beginning plan of clinical research to be performed. These clinical research projects encompass most of the major fields of dentistry.

NURSING DEPARTMENT

During the past year and one-half, the Nursing Section of the Research Facilities Planning Branch has become the Nursing Department of the Clinical Center.

With the appointment of additional nursing personnel, activities moved from a consultative to an operating phase with most of the activities directed toward (1) intensification of recruitment activities, (2) preparation of equipment lists, (3) development of the organizational structure of the Department, (4) preparation of job descriptions, (5) determination of staffing requirements, (6) collaboration with other departments in program planning, equipment listing, and (7) setting up Civil Service examination announcements, rating scales, vouchers, etc., for nursing positions.

A brief account of Nursing Department activities July 1, 1951--December 31, 1952, follows:

1. Planning Activities

Planning activities involved an extensive and detailed review of the structural and functional aspects of the patient-care facilities with recommendations aimed toward the achievement of maximum efficiency of operations and a high standard of patient care. This planning included:

(1) Determination of the adequacy of certain physical facilities together with recommendations for changes and improvement in areas such as: Operating Room Suite, Admissions and Follow-Up Department, Mental Health Children's Unit, etc.

(2) Recommendations regarding space allocation and space utilization in nonclinical areas.

(3) Development of detailed proposals for the organization and function of the Nursing Service including: Preparation of a statement of purpose and

functions; preparation of an organizational pattern, definition of responsibilities, lines of technical and administrative communication; preparation of material for budget estimates for fiscal year, 1953-54, including proposed staffing pattern, a comparative budgetary breakdown from representative hospitals, compilation of existing standards relative to nursing care; estimation of both nonprofessional and professional staff needs; and acquisition of materials for procedure and policy manual.

(4) Collaboration with other department heads of the Clinical Center on such matters as: Planning X-ray and urographic equipment and linen supplies, listing equipment for use in dental surgery, exploring training needs with the Housekeeping Department, and many others.

2. Selecting and Acquiring Equipment

Members of the Nursing Department staff have spent a large portion of their time in activities related to the selection and acquisition of Clinical Center equipment and supplies. Before lists could be compiled for the Procurement Section, equipment needs had to be determined through many staff conferences, consultations with experts in the field, visits to field installations and contacts with manufacturers' representatives. Once the equipment needs were determined, specifications were developed.

3. Staffing

Two major projects have been the concern of the Department during the past year--(1) the preparation of position descriptions for nursing personnel and (2) preparation of the Civil Service examination announcements for professional nurses, practical nurses, and attendants.

A number of position descriptions were written and forwarded for classification and grading either to the Civil Service Commission or the Division of Commissioned Officers.

Three members of the nursing staff were recommended and appointed to the professional panel to prepare the announcements of the nurses' examinations. This involved setting the requirements for each grade, preparing the draft of the announcement, the vouchers, and the rating scale as well as outlining a suggested procedure for setting up the registers for each grade.

Approximately 300 letters and telephone inquiries have been received from nurses interested in working at the Clinical Center.

Recruitment of personnel for key positions has progressed rather slowly, as every effort has been made to select for appointment the person best qualified professionally and personally.

The following persons have been appointed to the staff:
Chief, Nursing Department, Mildred Struve, September 21, 1951
Chief, Cancer Nursing Section, Elizabeth Walker, January 1, 1952
Chief, Admissions and Follow-Up Nursing Section, Kathryn Knight, February 1, 1952
Chief, Psychiatric Nursing Section, Gwen Tudor, March 1, 1952
Assistant Chief, Education and Training, Doris Bresnahan, July 1, 1952
Assistant Chief, Nursing Department, Ruth L. Johnson, October 1, 1952

These staff members and Miss Evelyn Gombert, Assistant Chief, Education and Training, have conducted many interviews with persons interested in a position on the Nursing Staff.

4. Other Activities

Members of the nursing staff served as chief nurses for the various National Institutes of Health laboratories converted to casualty hospitals for civil defense training purposes. This included planning the staffing, equipment and supplies, and the procedures related to administration of the building as a casualty unit; organizing, planning, and conducting a training program in civil defense care for National Institutes of Health personnel assigned to the respective buildings.

Nursing staff members participated in approximately 20 public information programs conducted by the Scientific Reports Branch, Special Events Section, for foreign visitors, university students, interagency and other professional guests. In this connection they conducted innumerable individuals and groups through the Clinical Center.

During the period of this report members of the department, in their official capacities, attended 11 professional meetings and conferred with appropriate officials in 11 hospitals, principally in the Washington area. Staff members also have been active in professional committees, panels, research teams, and as consultants to a large number of professional groups.

Staff members held faculty appointments to: Washington School of Psychiatry; American University Graduate School (temporary appointment) for a summer course in human relations in management, requested by the Defense Department.

PHARMACY DEPARTMENT, CENTRAL STERILE SUPPLY SECTION

This report covers the period February-December, 1952. Prior to February, 1952, the planning and consultation were carried on through the office of Dr. George F. Archambault, Chief, Pharmacy Branch, Division of Hospitals, who gave many hours of work and excellent planning prior to the appointment of the head of this department.

In February, Mr. Arthur W. Dodds was placed on temporary duty to order equipment and supplies for the pharmacy. This was a well planned and executed job which was completed in three weeks. Mr. Dodds is now Chief, Pharmaceutical Service, USPHS Hospital, Baltimore, Maryland.

In February, the present head of the Pharmacy Department was also ordered to the Clinical Center for temporary duty for ordering equipment and supplies for the Central Sterile Supply Section of the Pharmacy Department. During this time final specifications were approved for the Central Sterile Supply Section, both for Public Building Service and for National Institutes of Health purchase.

June 9, 1952, Dr. Milton W. Skolaut assumed full-time duties at the Clinical Center as Chief of the Pharmacy Department. Certain additional equipment was requisitioned, and expendable supplies have been readied for requisitioning during the remainder of the year.

Dr. John A. Scigliano was appointed Assistant Chief, Pharmacy Department, and will report in February, 1953. Mr. Joseph N. Salvino was selected as Chief, Central Sterile Supply Section, and will report in February, 1953. Other staff will be selected for assignment later.

At the annual convention of the American Pharmaceutical Association and American Society of Hospital Pharmacists held in Philadelphia August, 1952, the chief of the Pharmacy Department participated in various business sessions and was reappointed as a member of the Committee on Narcotic Regulations.

NUTRITION DEPARTMENT

The past fiscal year marked the activation of the Nutrition Department with the appointment of the chief September 1, 1952. During the last four months of this period, certain basic planning was undertaken to develop the department to a point where it would be able to undertake its responsibilities at the time of the planned opening of the Clinical Center.

Considerable time was spent during the calendar year 1952 in reviewing the physical layout of the department and in reviewing the specifications and the equipment that had been planned. A number of recommendations regarding physical changes were made to the Research Facilities Planning Branch. Most of these changes were minor since the chief of this department has made every effort to operate the department as it was first planned by the consultants.

An estimate of the quantity and kind of total equipment, including permanent equipment having a depreciation value after five to ten years of operation, as well as small equipment was developed. At the same time, an estimate of the approximate cost of purchasing equipment over and above that included in the contract was approximately $124,000. Up to the present time specifications have been written and about three-fourths of the total list has been let on contract.

The second step in planning was to develop a basic staff organization in order to plan a realistic budget figure. The Nutrition Department of the Clinical Center will serve the patient areas of each of the seven Institutes. The department, functioning in two major areas, will include a food-production and cafeteria unit and, secondly, a combined patient-serving and metabolic research branch which will involve the operation of eleven floor kitchens with decentralized food service and dishwashing facilities serving a maximum of fifty-two patients each. It is anticipated that a majority of the patients in the Clinical Center will be on a special diet therapy regime, each as a part of a specific research program conducted by the various Institutes. Planned also are eight special research kitchens, with one dietitian to each kitchen, providing for service to a maximum of ten patients. Only two of these kitchens, dealing primarily with constant diets, will be opened during the first year of operation. From this step, the staff needs in terms of nonprofessional employees was determined for each of the subunits of the department.

Recruitment of professional staff has moved along at a rather slow pace because it was considered essential that the organizational pattern and the graded positions be developed and the pattern accepted first. The recommendation was made that the total staff of dietitions be commissioned officer personnel. Other staff of the Nutrition Department are expected to come on duty the early part of 1953.

In collaboration with the personnel office of the Clinical Center, job descriptions for each of the one-hundred twenty-three nonprofessional employees were developed, and classification was made on the basis of these. Work was begun with the Board of Examiners of the Civil Service Commission located at the National Institutes of Health to develop an examination announcement to fill six nonprofessional positions within the department: Cook, general and metabolic kitchen cook; Baker, Meat cutter, Kitchen helper, general, and Food service aide.

Basic information was completed in order to substantiate our request for appropriation funds to support the raw food budget for patients and the budget for operating the cafeteria.

Up until this time, very little planning has been done with various directors of the National Institutes of Health.

The significant professional society activities that have been a part of the Nutrition staff have been as follows:

1. Presentation of paper entitled "Cooperative Planning of Dietary Services" to the Association of Military Surgeons of October 18, 1952, by Edith A. Jones, Chief of the Nutrition Department.

2. Attendance at the annual meeting of the American Dietetic Association on October 21-24, 1952, Minneapolis, Minnesota.

3. Program Chairman for the District of Columbia Dietetic Association.

4. Continued as Chairman of a National Project No. 3 for the Food Administration Section of the American Dietetic Association. The work of this Committee is to develop a bibliography of kitchen planning.

In summary, the Nutrition Department of the Clinical Center has spent the last four months in developing many of the basic pattern and procedures that will set the standard for its operation in 1953.

DIAGNOSTIC X-RAY DEPARTMENT

The early planning for the diagnostic X-ray service was carried largely by Dr. Jack Masur, assisted by consultants Dr. Henry Kaplan of Stanford University and Dr. Russell Morgan of the Johns Hopkins Hospital. Tentative floor plans for the diagnostic facilities and the darkroom were drawn up by the Westinghouse X-ray Corporation. By July 1, 1951, these plans were on paper and preliminary discussions had been held with Public Building Service officials concerning certain structural problems.

Late in the calendar year 1951 the present chief of the Diagnostic X-ray Department agreed to assist in achieving decisions concerning diagnostic X-ray equipment, darkroom accessories, and personnel requirements, and periodic consultation was provided during the latter part of 1951.

The present report covers the calendar year 1952. February 1952, the Chief of the Diagnostic X-ray Department agreed to serve in this capacity on a full-time basis effective July 1, 1952. In the interim he was to spend the major portion of his time as a radiologist at the Johns Hopkins Hospital devoting whatever time was indicated at the National Institutes of Health to assist in the planning and development of the X-ray department.

On February 11, 1952, specifications for X-ray equipment and for accessory supply needs were transmitted to Public Buildings Service.

Attention was next directed to the development of permanent plans for operation of the Diagnostic X-ray Department. Improvement in equipment and development of new equipment necessitated some construction and design changes within the X-ray department, such as the installation of a second high tension line for operation of a Schonander biplane cassette changer.

It was recommended that film identification be accomplished by using a small portable X-ray unit for film marking purposes, and plans for their construction were developed with the PHS electronics laboratory in Rockville, Md.

In the same manner it was decided that aluminum cylinders should be constructed for transportation of undeveloped film to the darkroom for processing, and plans were drawn up for their construction at the instrument shop of the National Institutes of Health.

Personnel and equipment requirements, as well as the budgetary needs for the operation of the X-ray department for the fiscal years 1953 and 1954 were developed. Other than the Chief of the Diagnostic X-ray Department, no personnel were employed during the calendar year 1952.

The Diagnostic X-ray Department was called upon by several governmental departments for consultation and service during 1952. The Chief of the Department served, upon request, as a member of the Radiation Safety Committee of the National Institutes of Health. He was also asked to serve as a consultant in radiology for the Outpatient Department of the Public Health Service at 4th and C Streets, N.W. On request of the National Cancer Institute, he agreed to review applications submitted to their organization for the loan of radium throughout the country.

During the month of December 1952, the Chief of the Diagnostic X-ray Department began the interpretation of all films taken in the Employee Health Service Branch at the National Institutes of Health. This service was provided at the request of Dr. Lynch, Medical Officer in Charge, Employee Health Service. Consultation was likewise provided to various Institute members involving X-ray film interpretation.

The Chief of the Diagnostic X-ray Department is a member of the faculty of the Johns Hopkins University and serves as a part-time radiologist at the Johns Hopkins Hospital. He had continued in this capacity until the time of the writing of this report. This hospital association has proved valuable and serves as a direct and ready means of consultation with Dr. Morgan and staff without fee and at the same time affords an opportunity of maintaining a clinical radiological experience.

During November 1952, an article entitled "Cardiac Mensuration by Roentgenologic Methods" was published in the American Journal of Medical Sciences. This article was written by Dr. Morgan and the Chief of the Diagnostic X-ray Department. During this same period, preliminary work was directed toward the assembling of data and the writing of an article on an unusual and rare type of congenital heart disease. This work is being conducted by Dr. Robert Cooley, Associate Professor of Radiology at Johns Hopkins Hospital, and the Chief of the Diagnostic X-ray Service at the Clinical Center. It is anticipated that this paper will be published sometime during 1953.

PATHOLOGIC ANATOMY SERVICE

At a series of meetings held in the Office of the Director, National Institutes of Health, during January 1952, the Pathologic Anatomy Service was organized, to consist of four sections: Surgical Pathology, Dr. Harold L. Stewart, Chief; Post Mortem Pathology, Dr. James H. Peers, Chief; Comparative Pathology, Dr. W. T. S. Thorp, Chief; and Histochemistry, Dr. R. D. Lillie, Chief. Dr. R. D. Lillie was designated also as chief of the Pathologic Anatomy Service, Dr. Harold L. Stewart as assistant chief, and supervisor of Histopathologic technical services.

Much of the floor planning and equipment selection for the Pathologic Anatomy area had been completed by a special ad hoc committee during 1950 and 1951, prior to the organization of the Service.

At a series of meetings held at intervals through 1952 (the period of this report), allotment of space for various diagnostic services in Wing A, 2d floor, was agreed upon, several revisions of the 1953-4 budget were considered, and allotment of personnel to various functions was settled; a list of outside consultants was selected and submitted to the Chief of Professional Services, Clinical Center. Space requirements for Histochemistry and for Comparative Pathology have been or are in course of satisfactory arrangement.

An area for frozen section diagnosis adjacent to the operating room floor has been allotted and equipment ordered.

A list of pathologists on duty or in process of employment at National Institutes of Health has been prepared, containing data as to qualification with the American Board of Pathology and experience.

Relations to Institutes and to National Institutes of Health--Office of Director

Dr. Lillie holds post of Chief, Laboratory of Pathology and Pharmacology, National Institute of Arthritis and Metabolic Diseases.

Dr. Stewart holds post of Chief, Laboratory of Pathology, National Cancer Institute.

Dr. Thorp holds posts of Chief, Laboratory Aids Branch, Office of Director, and Chief, Section on Comparative Pathology, Laboratory of Pathology and Pharmacology, National Institute of Arthritis and Metabolic Diseases.

Dr. Peers holds post of Chief, Pathologic Anatomy Section, Laboratory of Pathology and Pharmacology, National Institute of Arthritis and Metabolic Diseases.

Drs. Laqueur, Fisher, Fite, Habermann, Loomis, Highman, Bangle, and Longley serve as research workers in Laboratory of Pathology and Pharmacology, National Institute of Arthritis and Metabolic Diseases.

Drs. Hilberg, Congdon, Dunn, Edgecomb, Eyestone, Leighton, Murphy, Nadel, Schlyen, Steffee, Symeonidis, Velat serve as research workers in Laboratory of Pathology, National Cancer Institute.

Dr. Brecher serves also as Chief, Hematology Section, Clinical Pathology Service, Clinical Center, and as a research worker in Laboratory of Pathology and Pharmacology, National Institute of Arthritis and Metabolic Diseases.

It is contemplated that Dr. Thomas will form a research connection on his arrival at Bethesda.

Dr. Sokoloff is research worker in Laboratory of Pathology and Pharmacology, National Institute of Arthritis and Metabolic Diseases, and his relation to the Pathologic Anatomy Service is to be established on his arrival at Bethesda.

It is contemplated that Dr. Cristensen will also develop research interests and affiliation with one of the Scientific Institutes.

Relation to External Agencies

The diagnostic services to the U. S. Indian Service and the Bureau of Prisons, hitherto carried by Laboratory of Pathology and Pharmacology, National Institute of Arthritis and Metabolic Diseases, will be assumed by the Pathologic Anatomy Service.

SOCIAL SERVICE DEPARTMENT

From July 1951 to July 1952, no staff was assigned to this Department. During this period a report was prepared by Miss Cecile Hillyer, outlining the proposal for the structure and functions of the Social Service Department at the Clinical Center. Miss Hillyer had spent a considerable period of time visiting the outstanding hospitals of this country and obtaining detailed information about the functioning of their social service departments.

This report was available for the use of the director of the Social Service Department when he was appointed in July of 1952. The basic proposal was that a single integrated Social Service Department be established, making use of both medical and psychiatric social case-work services. A new position title and job description for program supervisors was recommended for the social workers who would be in charge of the case-work programs of the various Institutes participating in the Clinical Center.

Following the appointment of the Chief, Social Service Department, these proposals were reviewed with the administrative staff and the structure of the department was approved as proposed. Job descriptions were prepared for the various types of social service positions and were submitted for approval. The budgetary requirements for the department were estimated and justifications were prepared.

Recruiting was begun after the different positions in the department were approved, and potential candidates were interviewed for specific assignments. The structure of the department was established to provide social service coverage in four major areas: the National Heart Institute; the National Cancer Institute; a combined program of neuropsychiatry to include the National Institute of Mental Health and the National Institute of Neurological Diseases and Blindness; and the fourth area was a combination of the programs of the National Institute of Arthritis and Metabolic Diseases and the National Microbiological Institute. It was proposed that a program supervisor be assigned to be responsible for the social work program in each of these areas. It was recommended that social case workers with medical and psychiatric social work experience be assigned in these four areas of operations. An additional area of service was recommended so that social case workers would be available in the admissions program to provide assistance for individuals who sought admission to the Clinical Center but who were not eligible at the time of their application. It was anticipated that it would be necessary to provide a referral service to other medical installations which might care for such applicants.

During the period from July 1 to December of 1952, a beginning was made on the development of program and policies for the Social Service Department.

In December, the assistant chief of the Department was selected, Miss Ellen Walsh, case work supervisor at Saint Vincent's Hospital in New York City.

The space requirements for the Social Service Department were recommended and the provision for a central dictating system to be used by the casework staff was taken under consideration, and approval for such was recommended.

MEDICAL RECORD DEPARTMENT

Personnel, space, and equipment necessary for the Medical Record Department were considered early in the organizational plans for the Clinical Center. The chief of the Medical Record Branch, Division of Hospitals, Bureau of Medical Services, served as consultant regarding these needs. The present chief of the Medical Record Department accepted the position in April 1952. From the time of the first interview in 1951 until reporting for full-time duty September 15, 1952, she was able to devote part-time to the organizational plans of the Medical Record Department.

The responsibility of the Medical Record Department includes "development and direction of a system of medical records and statistical reports which will promote the best medical care of the patient and will meet the varied needs of the hospital and the several research Institutes of the National Institutes of Health, in providing basic data for medical research, evaluation of clinical services, planning and developing additional programs and activities, medical education, and other medical administrative and medico-legal needs."

In the organizational plans, these responsibilities have been divided into two sections: Medical record research service and medical record operation service. Each of these services will be directed by a well-qualified medical record librarian. Every step in the organizational plans has been directed toward the need of the Clinical Center--recognizing that this institution is unique and that procedures and systems must be tailor-made and not copied from another hospital.

The first meeting on medical records with representatives of the Institutes present was held May 2, 1952, almost a year prior to the anticipated opening of the Center. Basic principles of record and report systems were discussed. The following recommendations were considered:

1. Installation of the unit system of numbering records. (The same number is to be used for all admissions of the patient on the in-patient and out-patient services.)

2. Installation of a centralized record system. (All patients' records are to be filed in the Medical Record Department.)

3. Centralization of data pertaining to the clinical care of the patient. (All pertinent information pertaining to the patient is to be recorded on the patient's record.)

4. Installation of addressograph system. ("Charger plates" to be used for laboratory requests and headings on medical record forms. Other uses, e.g., index cards, are to be explored.)

5. Installation of follow-up system of patients discharged. All information obtained following discharge of patients should be considered a part of the unit record.

The Chief Medical Record Librarian attended the First International Congress of Medical Record Librarians in London in September 1952 and the Annual Conference of the American Association of Medical Record Librarians in Washington the following month. During the present year she is serving as President of the District of Columbia Association of Medical Record Librarians and is chairman of a committee for the American Association to survey the medical record librarian field. This survey is being conducted jointly by the American Association of Medical Record Librarians and the Division of Public Health Methods, Public Health Service. During the past eighteen months as an Analyst in the Division of Public Health Methods she has completed a monograph entitled Records and Reports of Local Health Departments--Criteria and Methods for Organization, Maintenance, and Use. This monograph will be published in the spring of 1953 by the Public Health Service. She is also serving as a member of the Task Force of the Division of Medical and Hospital Resources, Bureau of Medical Services, to develop standards for patient care in hospitals and related institutions.

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OFFICE OF THE DIRECTOR

July 1, 1951 - December 31, 1952

LABORATORY AIDS BRANCH

The research worker must be supported by a wide range of technical services, such as provision of culture media, experimental animals, animal caretakers, laboratory attendants, and scientific equipment developed in cooperation with the research worker. These aids to research require the services of technical and professional personnel capable of constructing unique precision instruments not available on the commercial market, of breeding animals of standard quality (necessary to controlled research studies) and of controlling disease outbreaks in the various animal colonies. These services at the National Institutes of Health are provided by the Laboratory Aids Branch.

The Branch provides central cleaning and sterilization of glassware for the laboratories and the Clinical Center, and is responsible also for the animal cage washing and sterilization facilities in the Clinical Center. A large quantity of mechanical equipment for glassware preparation and cage cleaning was installed during this reporting period to provide a more efficient operation with a minimum increase of personnel.

The Laboratory Attendant Section is a central facility which daily furnishes sterile glassware, fresh foods, and laundry to the Institutes. In 1952 the section processed 350 more tubs of glassware than in the previous year, with the same number of personnel. An employee of this section has been working with engineers in the Research Facilities Planning Branch toward mechanical washing of glassware and improvements in use of detergents. This section will be moved to the Clinical Center in 1953, where better facilities will be available and where it will function as a central glassware and cage-washing facility. Laundry and fresh food distribution then will be taken over by another branch. The Animal Section provides the laboratories with experimental animals, including animals of known genetic background.

During 1952 this section furnished to the laboratories 732,835 mice, of which 575,751 were general purpose and 157,084 had known genetic backgrounds. Twenty different strains of mice are produced at NIH. While mice are in most demand, the section also provided NIH researchers with 65,000 other experimental animals, including rabbits, guinea pigs, rats, and hamsters.

An inbred group of mice was taken over by Geneticist George E. Jay, National Cancer Institute, in 1951. During that year emphasis was placed on improving the strains and maintaining production for the Cancer Institute. In March of 1952 production began to increase, and by December 1952 it had tripled. The colony now is comparable in size and quality to any in the United States. In 1952 additional facilities were established at the Rockville Farm for maintaining dogs on long-term experiments for the Institutes, thus releasing valuable space in the animal areas of the NIH buildings.

As the result of efforts by an employee in the Animal Section to standardize animal cage design, the Institutes can now order cages by a reference number instead of submitting lengthy specifications.

The Instrument Section, in cooperation with the research worker, designs and constructs intricate scientific equipment that is not available in the commercial market. In 1952 there was a considerable increase in the amount of developmental work on equipment needed by the laboratories, particularly with respect to the Clinical Center.

A pipette washing machine was developed which cleans 160 pipettes at one operation, does a better cleaning job than any previous method known, but does not etch the glass in the operation. This has resulted in a considerable saving of man-hours and hundreds of dollars worth of pipettes.

A treadmill was developed for the Heart Institute for use by patients in a controlled temperature room.

The demand for electronic work in the Institutes has increased threefold, both in development of new equipment and repair of existing equipment, while the number of employees has remained the same.

The Media Section provides the laboratories with both stock and experimental media. Approximately 1,000 different media were prepared. There was also a growing demand for experimental media, due possibly to new research activities.

PERSONNEL BRANCH

The Personnel Branch is responsible for employer-employee relationships at NIH, as maintained within the framework of Civil Service Commission laws and regulations and Department and Public Health Service policies.

Personnel Generalists

Under the existing pattern of organization, most of the operating relationships among supervisors and employees and the Personnel Branch are conducted by personnel generalists who serve assigned organizational areas. During the reporting period, the personnel generalists completed more than 4,700 requests for personnel action.

Employment Section

The mission of the Employment Section is to employ and retain persons who will serve the best interests of NIH. To do this, a centralized interviewing service for applicants is provided and applications are maintained in a central file. Lists of applicants and employees eligible for promotion are furnished as needed. Current civil service examinations are also kept on hand. The Employment Section represents the NIH in negotiations on employment matters with the PHS, the Department, the Civil Service Commission, and other agencies concerned.

During the reporting period, the Employment Section completed a survey of the estimated appointments of civil service personnel made in 1952, detailing the kinds and numbers of persons needed and the approximate dates. The data is now being used in planning the NIH recruitment program.

Quantitative measures of the work accomplished follow: (1) Approximately 3,150 interviews with applicants; (2) more than 1,150 letters to applicants;

(3) more than 900 applications rated (exclusive of those rated by the NIH Board of Civil Service Examiners); and (4) nearly 750 certificates of eligibility received and processed.

Classification Section

The mission of the Classification Section is to see that NIH employees receive equal pay for substantially equal work by assignment to the work for which they are best suited. This is done by carrying out the legal and administrative requirements of the Classification act of 1949.

In July of 1952 the Classification Section and the personnel generalists initiated an annual inventory of all civilian positions so that classification of employees can be kept more current and salary inequities can be eliminated.

Measures of work accomplished follow: (1) Approximately 4,800 positions actions were taken; (2) more than 1,000 new positions were established; (3) approximately 600 positions were reviewed, and new descriptions prepared and classified for those not current or correctly classified.

Employee Relations and Training Section

This section has a threefold purpose: (1) To counsel and assist employees; (2) to provide a full range of employee services; and (3) to stimulate training opportunities for employees wishing to improve their skills.

Among the employee services available are: A transportation registry, information regarding housing, group hospitalization, incentive awards, retirement, and community facilities.

Orientation interviews are held with new employees; exit interviews are conducted to determine why employees leave; and training courses are stimulated as needed.

During the reporting period, the following sample work measurements were obtained: (1) More than 725 orientation interviews were conducted; (2) more than 310 exit interviews were held; (3) more than 850 listings of available housing were received; (4) more than 135 emergency loans were made from the NIH Recreation and Welfare Association loan fund; and (5) in the capacity of Secretary to the NIH Board of Employee Awards, the Employee Relations and Training Section participated in awards to 40 employees amounting to $3,665.

Performance Rating and Appointments Section

The major responsibility of this section is the auditing, preparation, and distribution of the official personnel journals which consummate personnel actions. Along with this responsibility are related operations such as inducting new employees, obtaining necessary forms, maintaining control records, maintaining the official personnel records, and preparing personnel reports. This section also has responsibility for the performance rating program.

During the reporting period, the Performance Rating and Appointments Section: (1) Completed a major conversion of its records to a uniform system; (2) effected the many changes required by a legislative amendment; and (3) computed the service and leave categories of all employees as required by the new leave Act.

Quantitative measures of work accomplished follow: (1) Nearly 5,400 personnel journals were written; (2) almost 1,100 new employees were inducted; (3) more than 2,000 periodic step increases were effected; (4) service dates were computed on 1,400 employees; and (5) nearly 1,900 performance ratings were obtained.

Board of U.S. Civil Service Examiners

Independent of the Personnel Branch, but an important unit in the total personnel program, is the NIH Board of U. S. Civil Service Examiners. This Board plans and conducts civil service examinations for the recruitment of personnel, establishes registers of eligibles, and issues certificates as requested.

In planning and preparing to meet demands for personnel, primarily for or as a result of activation of the Clinical Center, it was found necessary for the Board to prepare and issue 14 examination announcements, 10 reannouncements, and 5 amendments to existing examination announcements, and to establish 59 new registers, making a total of 202.

The Board also has screened and rated papers of 2,932 candidates, and conducted 287 written tests in which 962 individuals participated.

MANAGEMENT ANALYSIS

The activities of the management analysis staff in the Office of the Director, NIH, extend over the total range of activities of the Bureau. During the period covered, the staff studied and recommended measures leading to greater economy and efficiency in: (1) The conduct of extramural research programs; (2) the utilization of scientific manpower; (3) an intramural research laboratory; (4) central supporting services; (5) plans for operation of the Clinical Center; (6) training of laboratory workers; (7) basic Institute organization, and (8) many related problems.

A survey of the Grants Branch and Information Section of the National Heart Institute, and the Grants Branch and Training and Project Grants Section of the National Cancer Institute resulted in recommendations for changes in methods of organizing and carrying out the work, some of which have been accepted while others are still being considered.

A study of the utilization of scientists' time at NIH was conducted by a member of this staff who worked closely with a committee of scientists and research program administrators. As a result of the committee's work, a long-range study by the Survey Research Center of the University of Michigan has been undertaken to determine whether the NIH is using its scientific manpower as effectively as possible and what measures it should take to create and maintain a research environment in which the investigator can do his work most productively.

Other members of the Management Analysis staff developed and refined a procedure for recording and maintaining on punch cards complete information about space available at the NIH, whether laboratory, shop, or office.

A study was also made of the organization and methods of the Laboratory of Biologics Control, as a result of which changes were recommended in the utilization of staff members, in simplifications in handling certain aspects of the work, and reductions in the Laboratory chief's workload.

A system of work reports for most of the central service branches was also developed and installed to give NIH executives data on workload, backlogs and processing time. The report data have been used to compare each Institute's share of the costs of central services with its share of the services received.

The records management officer improved the records management systems in several Institutes, thus freeing 137 drawer file cabinets for re-use, and retiring 1,100 linear feet of records.

Working with the administrative officer of the National Microbiological Institute and with the audio-visual production service of the Communicable Diseases Center, a member of the staff developed and organized a program for training new laboratory workers in approved laboratory practice. A series of 6 training films, used as visual aids in this program, is in production. The first two of this series have been successfully completed and are available for use by all interested laboratories.

During the last quarter of calendar 1952, the administrative officers installed a new system for organized planning and follow-up of their biweekly meetings with NIH executive office. A member of the management analysis staff was a member of the agenda planning committee and executive secretary of these meetings.

Planning for the Clinical Center's organization and operations involved the total management analysis staff. They contributed to studies of its projected staffing, including organizational relationships, developed a method of assignment of space, worked out its location and direction indicators, and laid the groundwork for mail, messenger, and telephone services.

BUILDINGS MANAGEMENT BRANCH

The Buildings Management Branch is charged with:

1. Plant maintenance of the buildings, grounds, and facilities at the National Institutes of Health. This includes mechanical engineering (heating, ventilating, air-conditioning), electrical repairs, plumbing, metal work, painting, carpentry, and cabinet work, and automotive repairs.

2. Construction or fabrication of products needed for research but not readily obtainable through commercial sources.

3. Development of plans and specifications for alteration of existing areas and construction of new facilities.

The Branch operates a cabinet shop, a plumbing shop, a sheet metal shop, a paint shop, a machine and metallizing shop, a vehicle repair shop, electrical shop, and a mechanical engineering shop. It also has facilities for altering and constructing fixed laboratory equipment and additions to buildings.

This section also operates a transportation unit for trucking and hauling supplies and for furnishing passenger cars for official business.

During the reporting period, the Buildings Management Branch, like many of the other supporting services at NIH, expanded its program as the Clinical

Center and auxiliary buildings neared completion. Considerable time and effort were spent in planning space, personnel, equipment and supply requirements necessary for the maintenance and operation of the new buildings at NIH, including the (1) heating, refrigeration and incinerator plant; (2) shops, laundry and storage building; (3) Clinical Center; (4) grounds maintenance building, and (5) animal building.

Only a small portion of Building 10 is occupied at this time, but maintenance and operation services such as heating, electricity, etc., are being furnished the entire building.

The number of personnel on duty rose from 242 employees as of June 30, 1951, to 270 as of December 31, 1952. A sharper increase in personnel was expected to take place during subsequent months as new buildings are completed.

1. Mechanical Engineering Section

The heating plant, formerly located in the subbasement of Building 1, was replaced by the new heating, refrigeration and incinerator plant which, when completed, will occupy 101,475 sq. ft. This plant will furnish all heating, ventilating, and air-conditioning to all buildings on the NIH reservation with the exception of Buildings T-6, 16, and 16A, and officers' quarters, each of which have independent heating facilities.

2. General Services Section - Transportation Unit

With additional buildings to maintain, it is important that employees be able to get from building to building quickly. To avoid putting an additional drain on the Motor Pool, which has been reduced by eight (8) passenger vehicles in accordance with Section 705 of the 1952 Appropriations Act, Building Management Branch purchased ten tri-wheel scooters or package delivery units, known by the trade name of "Thrif-T". The vehicles were assigned to the shops with the greatest need for transportation, and in several instances released trucks to the Motor Pool, where they could be better utilized. Records have been maintained that indicate considerable saving in man-hours.

3. Grounds Maintenance and Landscaping Section

The more than 300 acres on the reservation, of which 98 are in lawn, received constant attention. Seeding, fertilizing, weed control, aerification, tree spraying, planting and landscaping are a few of the many jobs necessary to keep the grounds healthy and beautiful.

A grounds maintenance building for housing the considerable number of heavy and light equipment, such as tractors, a bulldozer, a small crane, power and tractor mowers, snowplows, etc., has been completed. With the acquisition of the new building, it is now possible to assemble and keep all equipment used by this section under one roof.

4. Plans and Specifications Section

In addition to its regular workload for plan specifications, drawing duplications, and sign making, the section was called upon to prepare tentative drawings for all fume hoods, walk-in cold boxes, and glass- and cage-washing equipment for the Clinical Center. Drawings for all cabinets and shelving for

Building 13; reference drawings of all underground installations, such as water and gas mains, manholes, and wiring; and complete drawings and specifications for the proposed air-conditioning of the older buildings on the NIH reservation were also undertaken.

5. Construction and Shops Section

This Section is composed of six shops: carpentry, paint, sheet metal, machine and metallizing, plumbing, and vehicle repair. In addition to the routine work of administering construction contracts and performing the general civil engineering duties, the Construction and Shops Section made preparations to occupy the new shops, laundry and storage building.

The move began November 24 and was completed December 19, 1952. For the first time, each shop has sufficient space to maintain all of its equipment and supplies.

The vehicle repair shop, which is responsible for the maintenance of all government vehicles on the reservation, has installed a new front end machine, the type found in automobile garages, for balancing front wheels of cars and detecting steering defects. This work previously was contracted for by local garages.

6. Electrical Engineering Section

Like the other units, the Electrical Engineering Section felt the impact of the expansion program that was unfolding at NIH. Handicapped by inadequate quarters in the basement of Building 1, the shop continued to give as efficient service as possible before moving to new quarters during December 1952.

Specifications and plans were prepared for a completely new fire alarm system for all buildings on the NIH reservation. The work, which was done under contract, is nearly completed. Numerous special lighting designs were worked out for the laboratories and for exhibits. An improved and complete public address system was installed in Wilson Hall. Numerous moves within the NIH made it necessary to install or relocate electrical wiring for lights and laboratory and shop equipment.

Fourteen new instruments were acquired for testing electrical equipment. Previously, it was necessary to return faulty equipment to the manufacturer, a procedure which meant a shipping expense but, more important, a delay in returning laboratory equipment to operating condition.

7. Administrative Services Section

This Section provides various types of administrative services for the Branch, including budgetary, purchasing and property, personnel processing and records, organization, management, communication, correspondence, and files. The expansion of activities at NIH has required an increased workload and the addition of 250 positions in fiscal year 1952.

It was necessary for the Section, in conjunction with the branch chief, to make a thorough study of the organizational structure of the branch and revise some areas to achieve a more efficient operating organization.

All existing position descriptions were reviewed, and in many instances revised. In addition, new position descriptions were prepared for new personnel.

Upon a recommendation from the General Services Administration Survey Team, preliminary steps were taken to establish and maintain perpetual inventory control records in the shop areas.

PURCHASE AND SUPPLY BRANCH

The Purchase and Supply Branch is responsible for the administration of the supply and property programs and policies of the National Institutes of Health. It is further responsible for the expansion and improvement of its standards in order to contribute greater service to the scientist and other operating personnel. The functions include purchasing, supply requirements, commodity standards, property accounts, property utilization, inventory control, storage, and issue of all property.

Purchasing

The vast volume of Clinical Center procurement necessitated the development of a rapid system of identifying, consolidating, and tabulating items appearing repetitively on requisitions representing the total requirement for the establishment and operation of separate laboratory units. To accomplish this, a system of numerical coding for identification was developed, and an IBM mechanical posting, listing, and sorting operation was adopted.

July 11, 1951, an emergency purchase procedure was established to facilitate the placement of orders covering emergency requirements. Under this procedure the requisitioner was not required to submit a requisition, but merely to telephone the emergency procurement clerk. Information was supplied by telephone, and availability of funds was determined through telephone contact with the Accounts Section. The order was placed with the vendor by telephone within minutes after the request was received. Delivery directly to the requisitioner was made to reduce the delivery time. A confirming purchase order was then supplied to the vendor. This procedure was utilized by all organizational units.

Under the agent cashier system, 1,385 cash purchases were processed. These transactions were restricted to emergencies, local purchases, to occasions when vendors were reluctant to accept government payment procedures, to cases where the vendor paid in cash, and in instances where it would be impractical to process payment by voucher.

To assist management in the problem of determining equitable charges against the various Institutes to cover central services, records were maintained relative to the distribution of workload, and reports were submitted monthly.

The training program for requisitioning and supply personnel of the Institutes, as well as the central office, was continued. During the period, three courses were conducted, of which two covered purchase, property and supply procedures and were comprised of ten one-hour weekly sessions. The third, a more detailed course in Federal Purchasing, consisted of fifteen one and one-half hour weekly sessions, of which eleven covered "on-the-job" training. These courses were well attended by representatives of virtually all Institutes.

The second annual Research Equipment Exhibit was held May 20-22, 1952, and attracted 2,181 visitors, of which 1,445 represented other government agencies, various hospitals, universities, and other organizations. Seventy exhibitors participated in this event and displayed approximately $270,000 in clinical and research equipment.

Property

April 10, 1952, a broad property program was approved by management. The first phase of the program was completed, namely the inventorying of the property of the Institutes and the reduction of the information to a written record. Conversion also was made of the acquisition records to the IBM punch card system, and there remains a reconciliation of this record with the inventory, the completion of which should give NIH a complete and up-to-date inventory record of all nonexpendable property in use.

With the completion of this phase of the program, the Property Unit launched the second phase, utilization. Meetings were held with the property custodians in each Institute to better acquaint them with their responsibilities and to inform them as to Property's part in the program. Constant and continued emphasis shall be given to the maximum utilization of property. We intend to utilize to the fullest the new inventory record so that the property custodians, laboratory chiefs, Institute directors, and the Office of the Director shall be fully informed concerning the status of equipment, the types of equipment on hand, in use, in storage, the original cost, and the present value, etc. Information thus derived from this record can be used for the preparation of budgets, forecasts in making new purchases, over-all dollar value of equipment, etc. We shall continue to expand and improve each phase of our property management program, institute new procedures, practices, and methods, and keep the Institutes and all employees informed as to new regulations and policies. The goal is maximum utilization of equipment and reduction in expenditures.

An office furniture and machine reconditioning program was established for resale of equipment to the Institutes for cost. Thirty-six desks, tables, 24 chairs, four bookcase sections, and 17 typewriters were reconditioned under this program.

A laboratory loan service was established January 1, 1952, to provide operating personnel with instruments and equipment for short-term loan. During the period January 1 through December 31, 1952, the Service made 71 loans to laboratories effecting a possible savings of some $25,000 in the purchase of new equipment. Thirty-three items of equipment are available, involving an acquisition cost of $17,500.

An employee separation procedure as it relates to property accounting was developed and established. Under this procedure an employee leaving the NIH is not given his final paycheck until relieved of any property accounting responsibility.

Central Supply

During the reporting period, the Central Storeroom and Stock Control Units were consolidated into a single Central Stores Unit, the back order system improved, a Warehousing Unit established, storage facilities increased, several forms revised and combined for the purpose of work simplification, and a new procedure for stock inventorying developed. Eight storage areas in Building T-6 were consolidated into a single unit under the Purchase and Supply Branch.

Shipping and Receiving

The impact of the Clinical Center procurement program was felt during this period. Supplies and equipment were received and checked daily as the volume became greater each month.

A record system was established in an effort to minimize losses and demurrage charges involving returnable compressed gas cylinders.

WORKLOAD FIGURES

Purchasing

Dollar value of purchases....................	$5,504,395
Line items processed.........................	72,488
Purchase orders issued.......................	19,877
Personnel costs per dollar value of purchases.	$ .029
Avg. no. days to process requisition.........	6.72

Central Supply

Requisitions processed.......................	17,623
Line items processed.........................	79,648
Dollar value of issuances....................	$ 603,416
Avg. no. days to process requisition..........	1.35
Inventory as of 7/1/51.......................	$ 291,529
Inventory as of 12/31/52.....................	468,915

Property

	No.	Value
Items turned in to surplus by Institutes.......	26,247	$60,463
Items reissued to Institutes..................	11,921	39,438
Items rec'd from outside agencies.............	6,810	12,404
Items disposed of to outside agencies..........	7,734	36,168
Items sold or traded-in.......................	119	7,818
Items sold on quarterly sale..................	112	2,964
Items disposed of as unserviceable............	530	491

Shipping & Receiving

No. packages received........................	118,372
No. packages shipped.........................	6,076
Over-all personnel cost per package handled....	$ .22

FINANCIAL MANAGEMENT BRANCH

The work of the Financial Management Branch is done in two sections -- the Budget Management Section and the Accounting and Audit Section. The Budget Section prepares budget requests, has an active part in apportioning, allocating, and managing appropriated monies, and makes analyses of present and future financial position. The Accounting Section accounts for monies expended and makes financial status reports by organizational units and by purpose. It prepares payrolls, audits the bills and certifies them for payment by the Treasurer of the United States.

At the beginning of this reporting period, activities of the National Institutes of Health were financed through five separate appropriations: Salaries, Expenses and Grants, National Cancer Institute; Mental Health Activities; Salaries, Expenses, and Grants, National Heart Institute; Dental Health Activities, and Operating Expenses, National Institutes of Health. The latter appropriation provided funds for the National Microbiological Institute, National Institute of Arthritis and Metabolic Diseases, and National Institute of Neurological Diseases and Blindness. It also financed central services (central administration, buildings management, laboratory aids, purchase and supply, and scientific reports) and the Clinical Center. Cost of these services and the Clinical Center were paid out of the operating expenses, NIH appropriation and a charge made to Institutes with separate appropriations for a pro-rata share of the costs.

In addition to these appropriations, a separate appropriation called "Construction of Research Facilities" was available on a no-year basis for financing construction, for initial equipping and purchase of a supply inventory for the Clinical Center, and for other new service areas.

Accounting for funds under these appropriations was geared primarily to allotment accounting for NIH activities, and within these, to project accounting based on cost analysis rather than a cost system. Budget, audit and payroll operations were geared to existing program levels - pre Clinical Center expansion.

During the reporting period, a number of significant developments have affected the work of the branch: the Clinical Center was nearing completion; recently established Institutes were expanding operations; all Institutes were preparing for the opening of the Center, and changes were occurring in government finance and supply operations.

As a result of changing conditions, the following developments occurred in the Financial Management Branch:

(1) The first budget for Clinical Center operations (1953) was presented to the Bureau of the Budget and the Congress, and funds were appropriated for this purpose.

(2) In line with recommendations of the House subcommittee on appropriations, and to simplify central accounting and budgeting, separate appropriations were established in the 1954 budget for three Institutes: Arthritis and Metabolic Diseases, Microbiology, and Neurology and Blindness, thus increasing the number of NIH appropriations from 5 to 8. The 1954 budget also reflects the impact of Clinical Center and related expansion for the forthcoming fiscal year.

(3) Staffing and procedural changes were made to meet an increased workload in budget; experiments were started to determine the feasibility of using tabulating equipment for certain aspects of budgeting.

(4) To get ready for the impact of expanded Clinical Center and related operations, changes and refinements in accounting and payroll procedures for existing programs were accomplished. Early planning also was begun on determining the feasibility of using tabulating equipment for payroll operations.

(5) To meet expanded and changing supply needs, a plan was prepared for financing central storeroom operations on a revolving fund basis. The 1954 budget contains funds for the financing of this plan and NIH Accounting and Supply personnel are working jointly on the necessary details for putting the plan into effect July 1, 1953. A General Accounting Office--General Services Administration task force working with NIH, PHS, and Department of Health, Education, and Welfare personnel--made the principal contribution in development of this plan.

(6) The task force also formulated recommendations on other aspects of supply accounting and finance which, if adopted, will have a great effect on accounting methods for stock and equipment located outside the central storeroom facility; for example, recommendations related to maintenance of perpetual inventories in many central service branches, and to establishment of general ledger central accounts for equipment in use.

(7) In consideration of a GAO recommendation that NIH finance central services (including Clinical Center) on a "fee-for-service" basis, and as a part of an NIH management improvement plan, the Financial Management Branch employed a task force approach to study the "fee-for-service" problem. This task force recommended and received approval of a plan to finance seven out of a possible 30 central service operations on a simulated "fee-for-service" basis beginning July 1, 1953, to determine the feasibility of this type of operation.

(8) To meet management needs and changing reporting requirements, new simplified statements of financial status were devised and combined with regular analytical reports of financial condition.

(9) To meet Clinical Center requirements as well as those of other government agencies for financial data the general outlines of a system of cost accounting began to emerge. With management needs and economy in mind, decisions were made to build on to the existing framework of organizational accounting for obligations and expenditures and project accounting through cost analysis, to obtain cost data in most areas. However, complete cost systems were deemed necessary for nutrition (including the cafeteria) and laundry activities and perhaps the pharmacy and certain other operations.

(10) To assist with accounting plans for expanded NIH operations, a full time "systems" man was assigned by the General Accounting Office to work with NIH personnel.

Appropriations for the National Institutes of Health provide funds for the following major program areas:

Program Area	Fiscal Year Obligations(in thousands)[1]	
	1952	1953 est.
General medical research	$ 5,398	$ 5,010
Arthritis and Metabolic Diseases	3,982	4,569
Microbiology	5,106	5,479
Neurology and Blindness	1,562	1,972
Cancer	14,416	17,519
Mental Health	9,831	10,819
Heart	9,653	11,775
Dental	687	724
Total obligations	$50,635	$57,867

Within the above appropriation and major program framework, funds are provided for the following activities:

Activities	Fiscal Year Obligations(in thousands)	
	1952	1953 est.
Grants for:		
Research	$17,583	$20,358
Training and fellowships	9,161	10,208
Control	8,118	8,550
Total grants	34,862	39,116
Direct operating funds for:		
Research	12,473	15,304
Training	71	70
Technical Assistance	1,150	1,143
Review and approval of grants	909	950
Administration	1,170	1,284
Total direct operations	15,773	18,751
Total obligations	$50,635	$57,867

RESEARCH FACILITIES PLANNING BRANCH

The present report summaries the status of Clinical Center construction as of December 1, 1952, and equipment planning and requisitioning phases of the Clinical Center and auxiliary structures as of November 1952.

December 1, 1952, Public Buildings Services construction engineer for the Clinical Center project reported two buildings completed and turned over to NIH - the radioisotope laboratory and the utilities building. Buildings 99 percent complete were the Clinical Center; shops, laundry, and storage building; grounds maintenance building; and chemical storage buildings. The boiler plant and incinerator was reported 80 percent complete; animal and dog kennel buildings, 70 percent complete; and the apartment house (quarters for staff of the Clinical Center who must be on call 24 hours of the day) 15 percent complete.

Because construction costs have been steadily rising since January 1948, certain undertakings have been reduced or deferred for the present.

1/ Exclusive of liquidating cash.

A tentative budget showing the dollar allocation for equipment and supplies, by principal categories of administration at the NIH was completed by Research Facilities Planning Branch November 1951. Firm agreements were then reached and a revised equipment allocation budget was issued February 15, 1952. This budget has since been used as a guide in the submission of all the Clinical Center Project's requisitions.

Problems encountered in the course of the Clinical Center planning have been varied. Projects which involved original investigations and development included chemical fume hoods for air-conditioned buildings, automatic animal cage washing machines, and mechanized operations for laboratory glassware cleaning.

A considerable variety of valuable reference material pertaining to building construction, machine design, air conditioning and ventilation, and equipment for hospital and laboratory use has been acquired by the Branch during the course of its operations. These materials were codified and filed for ready use whenever the need arises.

The correlation of special equipment designs with the structural facilities in the Clinical Center project has been an extremely important function of the Branch. For example, traffic tunnel and turnout designs, reciprocating lifts, and conveyor belts and pneumatic conveyors were initiated as a result of studies conducted in the Branch. Equipment designs were prepared (after consultation with Laboratory Facilities Planning Subcommittee, the chief of Buildings Management Branch, and many others) for laboratory bench equipment, chemical fume hoods, walk-in cold rooms and incubator rooms, glassware and cage washing equipment, and sterile transfer rooms. Detailed specifications were also developed for X-ray equipment and respiratory chambers.

May 4, 1951, a contract was negotiated by the Equipment Requirements Staff with a well-qualified interior decorator to color style the patient and public areas and to select appropriate furnishings for those areas. The decorator's recommendations were submitted July 16, 1951. The Equipment Requirements Staff has been primarily responsible for putting these requirements into effect by working closely with the contractor, Clinical Center and NIH staffs, and Public Buildings Services. The result of this action is that the Clinical Center will present a modern, yet conservative, and pleasing appearance, with furnishings purposely designed to depart from the usual institutional atmosphere.

By the end of the reporting period, equipment planning had progressed to a point where the remainder of the planning can be shifted to a direct operation between the various Institutes and the Purchase and Supply Branch. Accordingly, the Equipment Requirements Staff was dissolved November 19, 1952.

SCIENTIFIC REPORTS BRANCH

The Chief, Scientific Reports Branch, in addition to coordinating the information services of all Institutes, has the responsibility for general NIH press releases; speeches; TV and radio shows; the NIH Record; the wide range of central services to assist the scientists in the publication of their papers; maintaining the medical library and the Medical Arts Section, which serves all of the Institutes; operating the Translating Section, which is at the disposal of all NIH scientists for the translation of scientific papers providing editorial services for all of NIH; conducting tours for groups of visiting scientists and other visitors; and publishing the weekly calendar of events.

Fifty-four press releases, ranging in subject matter from the first synthesis of a pure form of vitamin B6 (important to research in cancer and other medical fields) and radioactive cortisone to appointment of Dr. James A. Shannon as Associate Director of NIH to succeed Dr. Topping, were either produced in the Institutes and cleared through the Branch, or originated within Scientific Reports Branch.

One thousand seven hundred and sixty-eight papers were submitted for presentation and publication and were reviewed and cleared through the Editorial Section. Approximately forty publications were edited and copy prepared, the format decided upon, and responsibility taken for the final printing.

The difficulties of internal communication in a rapidly expanding NIH have been solved, at least in part, by the semimonthly publication of the NIH Record. Through this medium, employees are kept informed of all activities - administrative, scientific, personal, and social - that directly affect them and their jobs. Special issues of the Record were prepared as training guides for the Civil Defense Rehearsals at NIH. The NIH Record has become increasingly valuable as an historical reference, being referred to more and more as a background source of information. The circulation has increased to 2,700 in the last 18 months.

The audio-visual section of Scientific Reports Branch was established in May 1952. Among the audio-visual materials produced and in use by all Institutes for the information and training of professional, subprofessional, and lay audiences are: Color slides on the Clinical Center; slides of architectural and engineering features of the Clinical Centers; slides highlighting history of the Public Health Service; and slides illustrating research activity in the various Institutes of NIH.

Responsibility for making arrangements for visitors singly or in groups and for arranging a suitable tour of NIH for them falls to the Special Events Section. Ninety groups (1,579 people) were conducted through NIH during the 18 months from July 1951 through December 1952. The Rockefeller Foundation Fellows, World Health Organization trainees, the American Federation for Clinical Research members, the Southern Society of Clinical Surgeons, and the Gerontological Society are but a few of the groups so accommodated. Two thousand four hundred and fifty-three individuals were taken on tours of NIH during this same 18 months' period. The nine annual lectures, open houses, and other special occasions are also handled by this Section.

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